

**Research Across Borders:
Proceedings of the International Research Panel of the
Presidential Commission for the Study of Bioethical Issues**

EXECUTIVE SUMMARY

Background

On October 1, 2010, the U.S. Government disclosed that it had supported research on sexually transmitted diseases in Guatemala from 1946 to 1948 involving the intentional infection of vulnerable human populations. In response, President Barack Obama directed the Presidential Commission for the Study of Bioethical Issues (the Commission) to “oversee a thorough fact-finding investigation into the specifics” of the U.S. Public Health Service supported research, and to conduct a review of current human subjects protection “to determine if Federal regulations and international standards adequately guard the health and well-being of participants in scientific studies supported by the Federal Government.” The President asked specifically for assurance “that current rules for research participants protect people from harm or unethical treatment, domestically as well as internationally.” President Obama directed the Commission to consult with its counterparts in the global community and to seek the insight of international experts as part of its work on contemporary protections for human subjects of research.

The Commission convened the International Research Panel as a subcommittee to advise the Commission on the President’s charge. The panel consisted of experts in bioethics and biomedical research from ten different countries including: India, Uganda, China, Russia, Brazil, Argentina, Belgium, Guatemala, Egypt, and the United States. The Commission charged the panel to undertake a consultation process to examine:

- a. The dominant norms, and competing alternatives, driving the ethics of medical research in different global regions outside of the United States;
- b. The conflicts, if any, between U.S. norms and international standards;
- c. The challenges facing researchers conducting U.S.-funded research in global settings; and
- d. Possible strategies to address differences in regional norms for medical research.

The panel met on three occasions to discuss research standards and practices in human subjects research around the globe. In their discussions the panel drew upon their individual expertise and decades of experience conducting research and developing standards and policy to protect human subjects. The panel’s deliberations were further informed by background literature selected by the panel members and Commission staff.

In shaping its discussions and formulating its findings and recommendations, the International Research Panel prioritized a set of critically important, fundamental issues for ensuring that the health and well-being of participants in scientific studies are well protected such as informed consent, risk reduction, risk/benefit analysis, community engagement, and review mechanisms. The panel prioritized these issues over other significant but more controversial ones in international research such as trial design, access to post-trial benefits, and the provision of ancillary care, topics about which researchers, ethicists, and international bodies currently disagree. Panel members sometimes offered specific views on these more controversial issues. But, considering the limited time available for their work, the group chose to focus on core, practical issues that, if improved, could more immediately enhance the well-being of human research subjects rather than on the more contentious topics currently under discussion in the research community. Panel members discussed examples of existing international consensus building bodies, such as the World Health Organization, that could address some of these more controversial issues as well.

The first panel meeting, convened in Philadelphia, Pennsylvania, in April 2011, focused on understanding existing standards and practices for conducting human subjects research around the world. U.S. standards and requirements were discussed for research conducted both domestically and abroad. Panelists presented an overview of legal and ethical standards and practices in China, India, Russia, Sub-Saharan Africa, Brazil, and Latin America more broadly. The panel reached agreement on the major issues they wished to address in future discussions.

The second meeting occurred in London, United Kingdom, in June 2011. The discussions focused on the following topics: economic context of research and global justice concerns; respecting diversity and community engagement; seeking unity and/or harmonization in transnational standards and universal principles; and regulatory reach, compliance, and enforcement. The panel concluded the meeting by drafting a working list of findings and recommendations.

The third and final meeting of the panel took place in Washington, D.C., in July 2011. The panel discussed two case studies of international research as an exercise to examine and identify best practices in international research. The panel then completed its list of findings and recommendations, which are included below. These findings and recommendations reflect the panel members' consensus opinion based upon available literature, meeting discussions, and their personal expertise. The summary proceedings of each one-day meeting are included in this report as well.

The International Research Panel presents the following findings, recommendations, and proceedings to the Commission to inform the Commission's response to President Obama's charge, which was limited to research funded by the U.S. Government. But, in the panel's view, the principles and practices to protect the health and well-being of human research subjects apply regardless of funding source. The panel believes that its findings and recommendations may have application to privately funded research as well.

FINDINGS AND RECOMMENDATIONS

Findings

- 1. Over the past five decades, the United States has made significant progress in developing rules, standards, and practices for protecting human subjects in research.** From legislative changes in the early 1960s¹ through to detailed regulations and specific policies for NIH-funded research today, the United States has played a leading, though by no means exclusive, role in shaping international and transnational standards to guard the health and well-being of participants in scientific studies. Transnational efforts to develop and improve upon U.S. rules, standards, and practices for protecting research subjects have also emerged, and collaboration between U.S. and international bodies has steadily increased over time.

Recent transnational standards reflect input from nations around the world, including the United States. Examples include the Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (1993, revised 2002), which specifically outline how the principles set forth in the *Declaration of Helsinki* can be applied in developing countries. In another example, the UNAIDS' *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials* (2007) provides "systematic guidance on how to effectively engage stakeholders in the design and conduct of biomedical HIV prevention trials."² These international efforts reflect a common goal of ensuring that clinical research can go forward under an ethical framework that promotes the rights and welfare of research subjects while advancing the goals of sound science.

- 2. 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.
- 3. Biomedical research is expanding around the globe, with an increasing number and frequency of trials outside the United States.** International research is both necessary and important to improve global health. Clinical research conducted globally can benefit many people. International research also increases the opportunity to address cultural, genetic, and economic variation as a contributor to health outcomes. In many countries, however, lack of infrastructure or cultural appreciation for what is necessary to adequately guard the health and well-being of research participants may result in gaps and risks that undermine not only the welfare of individual subjects but also the medical

research system in places where research is badly needed. Understanding of, and adherence to, the principles and practices governing ethical human subjects research by all, including the scientific community, ethics review bodies, and communities from which subjects are recruited, can enhance protections and facilitate opportunities for research to improve human health. Involvement of all parties, from development of the research protocol through to application of results, is critical. Capacity building and education efforts are crucial to ensuring that proficient ethics review committees can and do exist around the globe.

- 4. Community engagement is important to (i) demonstrate respect for host and collaborative communities by engaging them as partners in research, (ii) enhance understanding of how U.S. standards can be applied in other cultural contexts, and (iii) provide opportunities for ongoing oversight and monitoring of research activities.** Community engagement can consist of a broad spectrum of activities, such as community consultation, inclusion of lay community members on ethics review boards, and the formation of community advisory boards. Community engagement can be especially important to build trust or close the gap in power differentials between those conducting or sponsoring the research and the community. But community engagement is not a sufficient guarantor of ethical research, and it is a complement to, but not a substitute for, basic human subjects protection systems.
- 5. Individual informed consent or its moral equivalent, for example, surrogate consent for children, is always required in interventional clinical research with human subjects, and is universally regarded as playing a central role in protecting subjects, regardless of where research is conducted.** Exceptions to obtaining individual informed consent must be ethically justified. For example, current U.S. regulations allow consent to be waived when the research involves no more than minimal risk, the waiver will not adversely affect subjects' rights and welfare, the research could not practicably be conducted without the waiver, and, where appropriate, subjects are provided with additional information after participation.³ In addition, FDA regulations allow a waiver of individual informed consent in emergency research with specific restrictions. Obtaining informed consent may also be unnecessary in activities such as quality improvement and some varieties of public health research. In highly patriarchal societies, permission from a household head should not be construed as or mistaken for informed consent; and, therefore, allowing a man to consent on a woman's behalf as a substitute for the woman consenting for herself is not an appropriate exception to individual informed consent requirements.

Recommendations

- 1. Researchers must demonstrate respect for human subjects and their communities in all phases of clinical trial design and implementation. Recognizing other cultural standards and practices through community engagement is one concrete means of showing respect.** In addition to ensuring that the standard safeguards for human subjects in research are in place—such as obtaining informed consent, minimizing risk, and conducting independent review—researchers should engage with communities or

populations to be involved in the research. This engagement provides not only a local mechanism of accountability, but also a partnership in achieving the research goals. There is an emerging literature and global conversation concerning the means by which to properly engage communities.⁴ Open and inclusive dialogue is crucial to showing respect for communities, learning about context, responding to concerns, and working toward effective capacity building. Community engagement can strengthen and facilitate research while protecting subjects. For example, in a community in which written informed consent is considered inappropriate because of confidentiality issues, adherence to local traditions, or distrust of the signing process, researchers can explore together with the community other more acceptable methods of documenting informed consent that will meet regulatory requirements while respecting local norms.

Nonetheless, researchers cannot—and should not—accept uncritically everything that a community recommends or requests. Cultural standards and practices should be followed only to the extent that they do not conflict with basic universally recognized human rights. For example, some paternalistic cultures designate certain individuals to speak on behalf of the community. Although they may be important representatives of community interests, it cannot be assumed that they are always acting on behalf of individuals' rights and welfare.⁵

- **Ongoing international dialogue between U.S. and international bodies is critical to protecting human subjects in research.** Through such dialogue, the research community can share and learn from emerging successes and failures.
 - **U.S. and foreign investigators would benefit from clarification of the U.S. regulatory exception for foreign “protections that are at least equivalent to those” in the United States (“equivalent protections”) found at 45 C.F.R. § 46.101(h) and how it can be applied.** Recognizing equivalent protections is one way of respecting international standards and practices. For example, regulations in the U.K. do not require annual continuing review as U.S. regulations do,⁶ but many argue their regulations safeguard human subjects just as well. Similarly, some countries have human rights laws that offer protections for prisoners and other vulnerable populations that meet the same ends, if through different procedures, as U.S. protections.⁷ Recognizing equivalent protections would minimize the problem of U.S. insistence on procedural standards that may not offer more effective ethical safeguards for human subjects, or that may preclude research in countries where it could improve public health.
2. **Funders of human subjects research should support ethics training for investigators and others, including IRB members.** Researchers and others involved in human subjects research must be adequately educated and qualified to assess risks to the health and well-being of participants. Some members believe that qualifications of individual researchers and ethics review committee members should be confirmed by national standard setting organizations rather than research funders. All agree that training should address rules, standards, and practices as well as the ethical principles underlying them. Issues that arise in international studies are not always adequately addressed or cannot

always be resolved by following written rules and standards. Appropriate training can provide researchers and ethics bodies with greater insight regarding the deeper moral values at stake, enhance their capacity for ethical analysis and reasoning, and help guide ethical actions. Familiarity with principles, combined with experience, is among the best means for creating a shared culture of responsibility.

It is particularly important that host countries have competent ethics review committees in place to safeguard participants in research and that, when they do not, researchers and funders carefully consider additional steps to ensure that human subjects are protected. They must examine the quality and nature of local review—without unilaterally imposing their own systems—to ensure that the benefits of local review inure. Third-party ethics review groups, perhaps through the World Health Organization or another neutral group, could pre-review and/or monitor research as local capacity is improved.

- 3. Greater efforts are needed to enhance transparency, monitor ongoing research, and hold researchers and institutions responsible and accountable for violations of applicable rules, standards, and practices. To enhance transparency and accountability, governments should consider requiring all greater than minimal risk research to be registered and results reported.** Current U.S. law requires advance registration in a public database and the reporting of results for many clinical trials, but not all. It does not apply to non-clinical research, for example, observational and epidemiological studies.⁸ Similarly, the European Medicines Agency launched an online registry in 2011,⁹ which consists of information provided by sponsors of approved interventional clinical studies of medicines, as well as ethics committee opinions. The registry covers pediatric clinical trials and any Phase II-IV adult clinical trial recorded on EudraCT from both industry and research institutes. The World Health Organization now sponsors a Clinical Trials Registry Platform to link national and international registries across the globe, and many countries have established national registration requirements and registries.¹⁰
- 4. The United States should implement a system to compensate research subjects for research-related injuries.** One promising model might be based on the U.S. National Vaccine Injury Compensation Program, a no-fault alternative to the traditional tort system that provides compensation to people found to be injured by certain vaccines. The panel recognizes that there are a number of important policy issues that are implicated in developing a compensation system. The panel further recognizes that many countries and some U.S. research institutions have moved forward with developing compensation systems. For example, many European countries legally require sponsors and/or investigators to carry indemnity insurance for research-related injuries. In India, bioethics committees ensure that research sponsors pay compensation to participants injured in research. Brazil's bioethics regulations similarly ensure that research sponsors pay such compensation. The University of Washington, a U.S. research institution, uses a self-insured no-fault system to compensate participants for research-related injuries. The panel believes that compensation is an important issue to which the Commission should pay particular attention.

5. **Continued efforts to harmonize and guide interpretation of rules should be made a priority over creating new rules.** Shortly before the Panel's final meeting, the U.S. Government issued an Advance Notice of Proposed Rulemaking, signaling its consideration of revisions to U.S. regulations for human subjects protection. The U.S. proposal suggests a continuing need to review and refine existing regulations. More rules are not better, *per se*, but clear, sound, and streamlined rules can produce efficiencies and promote quality. New rules may be needed in the process of harmonizing existing U.S. rules and in countries with less developed systems in place. Harmonization of existing U.S. rules would add clarity to the oversight process.

Meeting One
April 8, 2011
University of Pennsylvania
Philadelphia, Pennsylvania

Members Present

Amy Gutmann, Ph.D., Chair
John D. Arras, Ph.D.
Julius Ecuru, B.Sc., M.Sc., Dip.IRE.
Christine Grady, R.N., Ph.D.
Dirceu Bartolomeu Greco, M.D., Ph.D.
Unni Karunakara, M.B., B.S., Dr.PH.
Nandini K. Kumar, M.B.B.S., D.C.P.,
M.H.Sc.

Sergio Litewka, M.D., M.P.H.
Luis López Dávila, M.D.
Adel A. F. Mahmoud, M.D., Ph.D.
COL Nelson Michael, M.D., Ph.D.
Huanming Yang, Ph.D.
Boris Yudin, Ph.D.

Members Absent

Peter Piot, M.D., Ph.D.

Opening Remarks

Dr. Gutmann, Chair, Presidential Commission for the Study of Bioethical Issues (the Commission), opened the meeting and discussed the reason for and purpose of the panel. In October 2010, the U.S. Government disclosed that its Public Health Service had supported research on sexually transmitted diseases in Guatemala from 1946 to 1948 involving the intentional infection of vulnerable human populations. In response, President Barack Obama directed the Commission to “oversee a thorough fact-finding investigation into the specifics” of the U.S. Public Health Service supported research, and to conduct a review of the effectiveness of current rules and standards governing research involving human subjects. Commission staff is conducting the investigation of the Guatemala experiments. President Obama further directed the Commission Chair to convene a panel of international experts to consider current U.S. Government regulations and international standards that guard the health and well being of participants in scientific studies supported by the U.S. Government.

The International Research Panel was convened pursuant to the President’s request as a subcommittee of the Commission to review and advise it on the matters described above. The discussions and conclusions of the Panel will be reported back to the full Commission.

Session 1: Legal and Ethical Standards and Practices – U.S. Overview

Legal and Ethical Standards for U.S. Government-Sponsored Clinical Research

Christine Grady, R.N., Ph.D.

Dr. Grady explained that U.S.-funded international research is subject to several statutes, regulations, and guidelines—none of which were in place at the time of the Guatemala experiments—including:

- The Common Rule (regulatory standard applicable to 18 federal research agencies);

- U.S. Food and Drug Administration (FDA) regulations and Good Clinical Practice (GCP) standards;
- International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) standards
- Clinicaltrials.gov reporting requirements;
- Funding agency-specific policies and guidance;
- Legal and ethical requirements of collaborating and host jurisdiction(s); and
- International guidance, for example, from the Council of International Organizations of Medical Sciences (CIOMS) and the Declaration of Helsinki.

In the United States, some of these documents have the force of law (e.g., the Common Rule, FDA regulations) and others have moral influence only (e.g., CIOMS, the Declaration of Helsinki). There are several challenges with these rules, including: their number and purview (e.g., federally funded research or FDA-regulated products); divergent interpretations of key terms (e.g., undue influence, minimal risk); substantive versus procedural requirements; gaps (e.g., what happens at the end of a trial, payment); and burdens of compliance. The compliance burdens can create an incentive for researchers to find the least arduous path to completing the research. Moreover, because of the panoply of rules, there is potential for lapses, and some researchers hire others to manage ethical concerns, therefore becoming less engaged.

The Common Rule, promulgated as such in 1991, applies to all research supported or conducted by any of 18 U.S. agencies, regardless of where it is conducted. The U.S. Department of Health and Human Services (DHHS), the major U.S. funder of biomedical research, codifies the Common Rule at Title 45, Part 46, Subpart A of the Code of Federal Regulations (45 C.F.R § 46(a)). The Common Rule contains procedural requirements (e.g., independent review by an Institutional Review Board [IRB], informed consent and ongoing review requirements), as well as substantive requirements (e.g., criteria for IRB approval such as risk/benefit ratio and selection of subjects), these standards are mirrored in regulations across the 18 Common Rule agencies. Other subparts within the DHHS rules address IRB registration and research with children; pregnant women, human fetuses, and neonates; and prisoners. The other Common Rule agencies, such as the Department of Defense may, or may not, have similar requirements for IRB registration and research with vulnerable populations.

The DHHS Office for Human Research Protections (OHRP) obtains assurance of compliance with these requirements through an agreement, called a “Federal Wide Assurance” (FWA), in which institutions, including U.S. federal institutions, that conduct or support U.S. Government funded research commit to comply with the Common Rule.

FDA, whose reach extends to institutions or individuals engaged in research with certain products (i.e., investigational drugs and devices), rather than with federal funds, is not a Common Rule agency. FDA’s human subjects protection regulations, found generally at 21 C.F.R § 50 and 21 C.F.R. § 56, also require independent review and informed consent but they differ in some minor ways from the Common Rule and include additional requirements. FDA was involved in the development of the ICH/GCP standards, as were its European Union and Japanese counterparts. These standards include provisions for informed consent and independent

ethical review. While the ICH/GCP standards apply as a matter of law in many countries, in the United States they serve only as guidance.

In addition to these standards, institutions and individuals undertaking certain FDA-regulated research must register their studies in an online U.S. database, known as ClinicalTrials.gov, which provides public access to basic information about study design and results. The registry serves both to facilitate recruitment and assure accountability. Established in 2000 with registration requirements only applicable to “clinical trials for drugs for serious or life-threatening diseases and conditions,”¹¹ the database expanded in 2007 to include statutorily required registration for most clinical trials of drugs, biologics, and devices. The 2007 law also established stiff monetary penalties for noncompliance.¹²

Agency-specific requirements for research include, for example, National Institutes of Health (NIH) mandates for (i) inclusion of women and children in most studies, and (ii) monitoring by a Data Safety Monitoring Board (DSMB) to assess safety in Phase 3 clinical trials and certain Phase 1 and 2 trials.¹³

The scope of the U.S. system covers most (but not all) public and private research with human subjects, ranging from surveys and observational studies to social science research and interventional trials. It also covers collaborative research that is conducted with international investigators in other countries.

In considering what the goals of oversight should be, Dr. Grady suggested that an effective system ought to: 1) assure a high quality of science and ethics; 2) contemplate harmonization of different rules and reduce unnecessary regulatory burden; and 3) include respect for rules of different jurisdictions (and permit them to govern when “equivalent protections” are in place), build or sustain ethics capacity, and ensure community engagement. Rules alone do not protect subjects, she noted. With regard to the concept of equivalent protections, she explained, the Common Rule has long permitted U.S. agencies conducting or supporting research in foreign countries with different procedural requirements to substitute the foreign standards for U.S. rules so long as “protections that are at least equivalent” to the Common Rule standards are applied.¹⁴ Unfortunately, she observed, the U.S. has rarely, if ever, exercised this authority and has failed to delineate criteria by which to determine “equivalent protections.”

Considerations for U.S. Government-Sponsored Clinical Research Outside of the United States

COL Nelson L. Michael, M.D., Ph.D.

Dr. Michael began by describing his 20 years of experience doing HIV vaccine development largely outside of the United States. Over that time, he has found three basic principles critical to ethical decision-making.

The first is host nation engagement, specifically, why is a research site selected? The site might be preferred for any number of reasons, including: prevalence of disease/condition under study; potential use of the product; appropriate national laws and policies; good intergovernmental relations; appropriate host national IRB oversight capacity; or logistics, including overall cost. If

cost is the overall driver, this raises concerns about whether the research is in the best interest of the participants and whether protections will be minimized in the interest of saving money. A real concern is who assumes the risks in the host nation.

A second principle is respect for partners. Studies should enrich host nation capacities and leave improved infrastructure. Important considerations are reasonable availability and access to treatment once the trial is done. Other factors are cultural sensitivity and regulatory compliance. With regard to cultural sensitivity, there can be enormous differences between and within countries. With regard to regulatory oversight, some countries have strong local authorities and weak federal governments. In others, it is the opposite. Although U.S. rules apply to federally funded research conducted outside the United States, U.S. scientists cannot dictate to host nation regulators how research should be overseen and monitored or how to reconcile differences between U.S. and host nation policies, especially with regard to licensing.

Dr. Michael said that his research efforts have intentionally supported the public objectives of the host nation Ministry of Health. Coordinating with the U.S. diplomatic, development, and health agencies is critical in establishing bilateral and multilateral research efforts. It is essential to seek the perspective and outlook of non-U.S. partners in international efforts. Building capacity—in both science and ethics—should be an obligation in resource-poor nations.

The third principle is respect for persons and communities. In poorer nations with inadequate access to care, should investigators be obligated to enable immediate public health impact and how can this be decided when local standards of care are poor? Should there be access to the test product after the study has been concluded and for how long should access be sustained? What is the obligation to enable the host nation to gain access to a beneficial product? Is it sufficient to simply refer to local standard of care or to endeavor to improve the local standard?

Dr. Michael concluded with several challenges for consideration going forward: 1) ensuring meaningful community engagement; 2) clarifying acceptable compensation for research volunteer participation; and 3) addressing intellectual property rights of research volunteers.

Discussion

All agreed that the standards described by Drs. Grady and Michael would have barred the Guatemala experiment. First, the Common Rule, FDA rules, if applicable, and international requirements for review by an independent IRB likely would have resulted in a finding of intolerable risks. Second, informed consent requirements from the same sources would have required individual consent or appropriate surrogate consent, for example, for children. Third, the DHHS rules for research with prisoners would have prohibited the work. These rules would have stopped the research before it started.

Moreover, scientific peer review and agency staff review practices today are a companion to and a check against less than adequate IRB review, were it to occur. It is unclear if the research would have passed tests for acceptable risk and scientific validity. In addition, many more host nations have oversight systems in place that did not exist in the 1940s. Other differences in today's environment include investigators who are more likely to have been trained in ethics or

regulatory requirements and “watchdog” or outside agents who are able to monitor research activities.

The point was made that there is a distinction between researchers observing populations engaging in risky behavior to understand various phenomena, and researchers intentionally exposing people to risky behavior and/or not treating them (e.g., the Guatemala and Tuskegee experiments).

Despite the existence of the standards that have emerged over the past three decades, not all international rules are the same, nor are they harmonized. In addition, rules can be interpreted differently or implemented by people who are either poorly schooled in ethics or overly dismissive of the need for ethical review or behavior. A host nation could make a decision to allow research that benefits only a very small segment of the population (e.g., higher socioeconomic status, political or economic interests) while putting a larger segment at higher risk. Populations in resource-poor areas might be willing to take on disproportionate risk and might be unable to provide informed consent. Informed consent alone, even among those with capacity to consent, is not sufficient to protect subjects. All of these factors demand due diligence and careful consideration.

One persistent challenge is the tension between procedural and substantive requirements of informed consent within and across borders. Institutional liability concerns often yield informed consent documents that obscure the simple explanation of a study and its risks and benefits.

The existence of many sets of standards also may preclude clinical research in countries where it is desperately needed; for example, research on sleeping sickness in parts of Uganda. Discussion arose about the level of standards required, for example, higher order principles or detailed procedures; who should set these levels, in particular, GCP guidelines or other transnational standards; and the importance of making cross-border rules manageable and useful within different locales. Development of international standards must involve wide consultation. Even when universally agreed upon, principles are not applied universally.

Session 2: Legal and Ethical Standards and Practices – International Overview

Ethical and Legal Standards and Practices – Indian Overview

Nandini Kumar, M.B.B.S., D.C.P., M.H.Sc.

Centuries-old Indian classical texts and medical codes of conduct as described in Siddha and Ayurveda, traditional medical systems of India, emphasize the “do not harm” principle, which is also the basis of modern ethics guidelines. Indigenised Unani medicine, originally adopted from Hippocratic dictums and influenced by Islamic perspectives, also enunciates similar duties and responsibilities of physicians.

Many factors make India an attractive place to conduct clinical research. India’s population was 1.15 billion in 2010, with a growth rate of 17.64 percent (which decelerated in the decade 2001-11). It is a heterogeneous population in terms of ethnic groups, tribal populations, and genetics. There is a large fraction of treatment-naïve people in the general population. India is the largest

English speaking country in South Asia. It also has a large and well-established university and health care system that participates in a vast research enterprise. The liberalization of economic policies in the 1990s opened the door for investment in India's pharmaceutical and biotechnology industries. A National Health Policy (2002) and a Science and Technology Policy (2003) relate to research priorities. The National Health Policy highlights the need to adhere to guidelines on research ethics, particularly in emerging research areas such as genetics, genomics, and stem cell research. The Indian Council on Medical Research (ICMR), with multiple institutes, is the oldest government research organization. It is also one of the largest such organizations.

ICMR issued the *Policy Statement on Ethical Considerations Involved in Research on Human Subjects* in 1980. Among other things, it addresses research on children, the mentally disadvantaged, and those with diminished autonomy. This statement has been revised twice, most recently in 2006. Based on international guidelines and local cultural requirements, it mirrors the provisions of U.S. policy in many ways, particularly those concerning review by an ethics committee and informed consent. Other guidelines by ICMR include those related to stem cell research and therapy (2007), and draft guidelines for biobanking, mental health research, and data set protection. Additional guidelines by other national agencies include those for gene therapy (1998), genetics and genomics (1999), GCP (2001), and draft guidelines for research related to disaster situations and compensation for research-related injury.

The Drugs Controller General of India (DCGI) (equivalent to the U.S. FDA) received 314 applications for clinical trials in 2010 and approved 237. Registration of clinical trials in India's clinical trials registry became mandatory in June 2009. As of April 2011, the registry included 1,664 projects. A number of regulatory agencies enforce a wide array of laws relevant to human subjects research. The Biomedical Research Authority, envisaged in the draft bill on ethical guidelines, shall play a role similar to that of the U.S. Office for Human Research Protections (OHRP).

Dr. Kumar noted that the composition and procedures of ethics review committees has improved over time, following efforts to increase training and monitoring. However, persistent ethical challenges include:

- Assuring informed consent and assent (in pediatric trials);
- Acceptance of local cultures;
- Concepts of autonomy in terms of family and community influence;
- Lack of engagement of local communities;
- The quality of IRBs;
- Compensation issues;
- Benefit sharing;
- Privacy;
- Conflicts of interest;
- Application of Indian law overruling international requirements in conflicting situations;
- Application of interpreted data to local populations; and
- Monitoring.

Biomedical Research in Russia: Issues of Regulation

Boris Yudin, Ph.D.

Russia's focus on medical and research ethics dates back to *Physician's Notes* published by V. Veresayev in 1901. A 1936 statute on medical research included requirements for consent, preclinical animal studies, and detailed documentation of methods. Today, relevant Russian policy includes the Constitution of the Russian Federation, federal laws, orders from the Ministry of Health Care and other agencies, and institutional policies. Federal laws prohibit research on persons deprived of liberty, and require voluntary informed consent, among other provisions. However, Russia has no full-fledged legislation specific to non-clinical research studies, meaning all human subjects research except drug studies.

In 2005, the Commonwealth of Independent States (CIS) (of which Russia is a member) developed a model law on "Protection of Human Rights and Dignity in Biomedical Research in the States." A draft law, "On Biomedical Research," was submitted to the State Duma in 2007 but was not supported.

Dr. Yudin said that there are no universally accepted procedures for approval of research projects outside of drug trials and it is impossible to know how much non-pharmaceutical research is being conducted. In addition, there are no reliable data about the number of IRBs, their composition, functions, or authority. In contrast, federal laws regulating medical drugs are in place, as are Good Clinical Practice guidelines that are similar to ICH/GCP. Roughly 67 percent of clinical trials in Russia in 2009 were conducted by foreign sponsors. According to ClinicalTrials.gov, there were 1,560 clinical trials in Russia from January 1, 2001 to January 4, 2011 conducted by U.S. sponsors, including NIH. FDA conducts inspections for U.S.-sponsored studies.

More than 1,000 research sites were accredited by the Roszdravnadzor, the central oversight committee. In 2010, a law was passed transferring ethical review of clinical trials to the Ministry of Healthcare and Social Development. This change was made to lessen the potential for undue influence and corruption of the review process. Among other things, after adoption of the law, all research sites must be accredited anew. Dr. Yudin said the new requirements have slowed the number of trials being conducted, in part because, as some experts in Russia believe, the new review process does not adhere to ICH/GCP, which, in their view, will lessen protections.

Dr. Yudin said there are two primary concerns among the public with the current system: 1) possible exploitation of subject populations by foreign companies, and 2) the quality of the clinical trials and undue influence of companies on the outcomes.

Legal and Ethical Standards and Practices in China

Huanming Yang, Ph.D.

China's large population, good medical and research infrastructure available at substantially lower cost, and a growing domestic pharmaceutical market make it an attractive place for clinical research.

Three major developments have changed the research environment: 1) increasing research investment, 2) more international collaboration, and 3) larger-scale research. China has heavily increased its investment in R&D, with spending growing by 20 percent per year since 1999, reaching more than US\$100 billion a year today (or 1.44 percent of GDP in 2007). China is also turning out huge numbers of science and engineering graduates, with 1.5 million leaving its universities in 2006. China intends to increase its spending on R&D to 2.5 percent of GDP by 2020. It is actively promoting clinical trials, seeing them as an important way of building research capacity in China, a strategic way to ensure investment and improve medical treatment as well as the domestic pharmaceutical industry in China, and a means to bring in scarce resources to support medical infrastructure and expensive medical treatments. Currently, China benefits a lot from international collaboration.

China's oversight of human research is improving, and is based on the Nuremberg Code, the Declaration of Helsinki, and UNESCO guidance. China also has a growing list of regulations that apply to clinical drug development, genomics, stem cell research, biosafety, and misconduct. The Ministry of Health issued regulations in 2007 on ethical review of biomedical research involving human subjects.

Discussion

Dr. Yang said that oversight is most intense when China is collaborating with international partners, especially the U.S. NIH and the U.S. Centers for Disease Control and Prevention. Transgressions that might have occurred years ago are no longer occurring because of the public's increased awareness, and Chinese scientists' and institutions' increased exposure to ethics concerns. However, it is not clear that rules are adhered to with the same intensity when only Chinese researchers and/or sponsors are involved.

Dr. Kumar noted that implementation of the rules in India is hampered by lack of adequately trained personnel and irregular interpretations by ethics committees.

Dr. Yudin added that there have been some audits of research facilities in Russia that have found spotty compliance.

Session 3: Legal and Ethical Standards and Practices – International Overview

Legal and Ethical Standards and Practices – Sub-Saharan Africa

Julius Ecuru, B.Sc., M.Sc., Dip.IRE.

Sub-Saharan Africa has a population of 819.3 million with a GDP per capita of US\$ 624. Life expectancy is 52 years and most countries spend less than 0.5 percent of GDP on R&D (except South Africa). The number of research projects has tripled in the last 10 years; 65 percent of which involved human subjects. Clinical trials were about 10 percent of the total, mostly funded from abroad and focused on communicable diseases.

The paradigm for research shifted in the 1980s with the HIV/AIDS epidemic. Prior to that, oversight was more focused on promoting research of national interest, with an emphasis on

control and coordination. The HIV crisis triggered increased global interest in understanding HIV, with increased vaccine and drug research efforts, which highlighted sensitive cultural and social issues. Thus, the growth of bioethics discussions in the region was not so much a response to scandals but rather a response to growing crises.

For most countries, guidelines and regulations are based on international guidance such as the Nuremberg Code, the Helsinki Declaration, CIOMS, the U.S. National Commission's Belmont Report (1979), ICH/GCP, and the U.S. Common Rule. In addition, constitutional provisions in some countries provide the overarching framework, for example, the Bill of Rights in South Africa. The guidelines in most countries are relatively recent, and they are just that, guidelines. Even so, the guidelines address issues of autonomy, beneficence, and justice.

Mr. Ecrú said that emerging issues focus on latecomers, that is, the national drug authorities becoming more involved in clinical trials regulations that might have conflicting roles with research ethics committees. Other concerns focus on more bureaucracy and tiers of research approvals. Competition to host multicenter trials is offered like "bait," which exerts pressure on regulatory processes. Finally, the many rules, differences in interpretation, and balance between research progress and human subjects protections leads to questions of whether countries are over or under regulating.

Legal and Ethical Standards and Practice for Research Ethics in the Latin American Region
Sergio Litewka, M.D., M.P.H.

Brazil, Argentina, Mexico, and Peru are the main players in the Latin American research environment, according to ClinicalTrials.gov. Most research is funded by international organizations and pharmaceutical companies. With the exception of Brazil (which invests at a higher rate), most Latin American countries invest about 0.5 percent of their GDP in research.

Argentina has a regulatory framework that reflects international guidelines. However, they are provisions, not laws, and there is no punishment for violation. Countries such as Bolivia, Columbia, and Chile have relatively new policies in place but do not have a solid framework for implementation. All clinical trials in Costa Rica have been suspended since 2010 in response to irregularities found in vaccine trials. Other countries have minimal laws on the books, some of which are relatively vague, related to general articles, or more aspirational than operational. Panama recently created a National Research Bioethics Commission.

Persistent concerns include:

- Lack of mandatory training in research ethics and the responsible conduct of research, and a perception that bioethics is an esoteric activity disconnected from research;
- Identification and management of conflicts of interest;
- Enforcement of existing regulations;
- Competence, composition, independence, and operating procedures of research ethics committees;
- Weak or inconsistent institutional accountability;
- Economic disparities and access to healthcare; and

- Governance and perceptions of corruption.

The Brazilian Research Ethics Infrastructure

Dirceu B. Greco, M.D., Ph.D.

Brazil is the largest country in Latin/South America, geographically and population-wise. It has 190 million inhabitants and ranks 7th in world economic power. It has a well-established Research Ethics Commission (CONEP), which is independent and accountable to the National Health Council. CONEP is responsible for reviewing all ethical aspects of research involving human subjects, as well as adapting and updating pertinent guidelines and norms. It exercises oversight for publicly and privately funded human subjects research of all types. It always reviews certain types of studies, for example, those dealing with human genetics, human reproduction, pharmaceutical products, externally sponsored research (public and private), and research with indigenous populations (approximately 10 percent of all studies, or roughly 1,000 annually). Most reviews, however, are conducted by roughly 600 local committees, which are registered with CONEP. CONEP also maintains a database of all trials, clinical or otherwise. All sites conducting human subjects research must have an ethics review committee approved by and registered with CONEP.

Brazil has had a resolution in place since 1996 setting national standards and guidelines for research involving humans. The rules have evolved over time in response to the changing environment. In 1997, a resolution passed requiring that research protocols must include provisions for access to the medicine being tested if it is proven to be superior to conventional treatment. A 1999 rule focused specifically on research protocols with foreign cooperation. Brazil opposed a 2008 revision to the Declaration of Helsinki that would allow the use of placebo designs when there is no available proven treatment in a region. A 2008 standard from the Brazilian Medical Council prohibits the participation of physicians in research projects where placebo is included in circumstances for which an active control exists, anywhere in the world.¹⁵

Dr. Greco said that the challenges of consent, vulnerability, and relevance of research are perennial challenges. Research performed in resource-constrained countries should provide volunteers with the best-proven medical care, which is difficult to implement despite Brazil's commitment to that principle. Restrictions on the use of placebo in the control arm of a study can be complex, but it is possible to perform scientific research without it. Building the appropriate infrastructure prior to the trial and then ensuring post-trial access requires prior planning and establishment of social support and local control.

Discussion

Uganda recognized the need for an oversight framework and now conducts routine and periodic monitoring. Twice monthly, teams go out to monitor sites. One of the conditions of accreditation is for ethics committees to have a monitoring plan in place.

Other concerns were raised about industry practices regarding publication of results, especially failure to publish negative results. In the United States, ClinicalTrials.gov registration and results reporting mediates this issue to some extent.

Session 4: Roundtable and Discussion

Dr. Gutmann asked the each member to discuss the most significant commonalities or gaps among standards or practices. The following issues were identified, though consensus was not sought or reached on particular items.

- Despite the importance of international norms, universal norms will inevitably result in different results in different circumstances, both among countries and within countries. Given the rapid rate of growth of international collaborative research efforts, it might be necessary to have another declaration of universal norms (e.g., the Declaration of Helsinki). However, it should be noted that the United States has not signed on to all universal standards, including the Declaration of Helsinki.
- There might be value in, at the least, defining a meaningful set of fundamental values that can be universally agreed on and adopted—how each country implements them might differ. Such discussions must ensure a seat at the table for all interested parties.
- It is important to focus not only on rules and guidelines but also how they are interpreted and implemented. This calls for a systematic effort to understand how guidelines are implemented so they can be made more effective.
- Concrete ways to demonstrate respect for others, such as recognizing cultural norms, should be found. This requires a framework for good participatory practices to ensure meaningful community engagement.
- Funders/sponsors should support ethics training as well as research. Training should be mandatory.
- An international registry should catalogue international research collaborations to facilitate monitoring and accountability.
- An international structure to evaluate problems that arise in the interpretation and implementation of principles with the goal of issuing common interpretations or guidance should be established.
- A regulatory framework to improve monitoring of ethics review committees should be adopted.
- The connections between research ethics and global justice, for example, issues of ancillary care and post-trial access to the benefits of research, should be recognized and evaluated.

Summary and Closing Remarks

Dr. Gutmann summarized the sense of the panel on the following points.

Where they exist, current guidelines are sufficient to ensure human subjects protections if they are appropriately implemented. Existing standards generally include the same basic principles of protection, for example, informed consent and independent prior review. More guidelines, *per se*, will not help except in those countries without rules in place. In fact, for some research activities in some places, fewer guidelines might be better because the current rules have become overly burdensome and somewhat conflicting from a procedural perspective.

There is inherent complexity in the oversight system because of the many types of research activities. Some experiments entail higher risks and therefore must meet a higher standard. The challenge is in ensuring that the level of oversight is appropriate for the study, that is, research activities are not being over or under regulated.

There might be opportunities for better communication not only within the United States but also with international partners to discuss policies and practices. One topic for discussion could be the concept of equivalent protections.

With regard to equivalent protections, U.S. and foreign investigators would benefit from clarification about what that term involves and how it can be determined. Closer attention to defining and recognizing equivalent protections is one way of respecting international norms.

Greater efforts are needed to monitor ongoing research and hold researchers and institutions responsible and accountable for violations. Although many journals require some assurance that ethical standards were adhered to during a research study, not all publications require that validation and industry-sponsored research might never be published.

If the U.S. Government is going to sponsor trials in countries that do not have a national framework, it should ensure that the protocols, reviews, and participation on the ground meet high standards. As an example, the World Health Organization has a pre-qualification process before a study can begin to ensure that regulatory standards can be met. The U.S. FWA process also warrants review to ensure it is achieving its goals when U.S.-sponsored studies are conducted abroad.

The United States needs to be cognizant of the needs and norms of developing countries in any discussions about universal standards and treat those nations as equals.

The full Commission will convene again May 18-19, 2011, in New York, New York, in a public meeting.

This International Research Panel will convene for a second time June 23, 2011, in London, United Kingdom, and for a final meeting in Washington, D.C., in July 2011.

The full Commission will receive a final summary of this Panel's proceedings for consideration at its August 2011 meeting. Its final report will be issued in December 2011.

Meeting Two
June 23, 2011
London School of Hygiene & Tropical Medicine
London, United Kingdom

Members Present

Amy Gutmann, Ph.D., Chair
John D. Arras, Ph.D.
Christine Grady, R.N., Ph.D.
Dirceu Bartolomeu Greco, M.D., Ph.D.
Nandini K. Kumar, M.B.B.S., D.C.P.,
M.H.Sc.
Sergio Litewka, M.D., M.P.H.
Luis López Dávila, M.D.

COL Nelson Michael, M.D., Ph.D.
Peter Piot, M.D., Ph.D.
Huanming Yang, Ph.D.

Members Absent

Julius Ecuru, B.Sc., M.Sc., Dip.IRE.
Unni Karunakara, M.B., B.S., Dr.PH.
Adel A. F. Mahmoud, M.D., Ph.D.
Boris Yudin, Ph.D.

Opening Remarks

Dr. Gutmann, Chair, Presidential Commission for the Study of Bioethical Issues (the Commission), opened the meeting and reminded the panel of the two overarching questions that President Obama has asked the Commission to answer: 1) to what extent do current rules and practices in U.S. Government sponsored international research protect people from harm or unethical treatment; and 2) what, if anything is needed to improve those rules and practices? Dr. Gutmann added that the panel may choose to deliberate on more than those two issues, but that those questions must be addressed.

Dr. Piot, panel member and Director, London School of Hygiene & Tropical Medicine, welcomed the panel to the London School of Hygiene & Tropical Medicine and gave a brief description of the school and its international research programs.

Session 1: Economic Context and Global Justice Concerns

John D. Arras, Ph.D. and Peter Piot, M.D., Ph.D.

Dr. Arras opened the session by focusing on several questions posed to the panel:

- Should legal and ethical standards and practices be the same in resource-rich and resource-poor settings? What is the role of economic context?

He said that it is important to recognize that clinical research takes place against a backdrop of massive global inequality; thus, everything is colored by that injustice. In considering issues of justice, ideal theory can help one envision the ideal objective—in essence, a description of “paradise island.” However, trying to implement ideal norms of justice in the midst of massive injustice can make things worse, as one pursues the perfect at the expense of the good. In contrast, non-ideal theory can facilitate decision-making in the midst of massive injustice, although it runs the risk of lowering the ethical bar to match the conditions on the ground. Nonetheless, both frameworks can guide us toward a better society.

Discussions of justice in clinical trials often center on the standard of care. Universalists believe there should be a global standard for everyone, rejecting moral relativism and the use of double standards. The problem with the universalist approach is that it may preclude important research, making it impossible to do certain types of research in places that might benefit. In contrast, uncritical contextualism is highly attentive to local nuances regarding sustainability, feasibility, and economic context, essentially making the local context—regardless of massive injustice—normative. This approach sets the parameters of ethical behavior based on the local context. This was one of the primary justifications used by the scientists involved in the Tuskegee syphilis trials.

A middle approach embraces a broader interpretation of the concept of clinical equipoise in which several local factors are considered, such as valid science, sufficient social benefits, and a favorable risk/benefit ratio. This approach, called critical contextualism, does not rely on moral relativism; rather, it sets standards that have to be interpreted in the local context (i.e., the highest sustainable standards for a defined population).

- What is the relationship between ethics and global justice concerns?

This question primarily relates to—over and above ethical research design (e.g., informed consent, ethical subject selection, favorable risk/benefit ratio)—what do researchers and sponsors owe to research subjects and their communities? There are several bases for various justice claims:

1. *The doctor-patient relationship*: It is unethical to abandon patients once one has started them on a regimen that improves their health.
2. *Reciprocity and avoidance of exploitation*: Individuals and their communities make sacrifices and undertake risks; therefore, they deserve adequate compensation for their efforts.
3. *Global distributive justice claims*: A global “basic structure” of society exists that allocates peoples’ life chances. There should be equal opportunity for all people, regardless of where they are born.
4. *Rectification for past and ongoing harms and injustices*: The global network of economic relationships, treaties, and policies systematically disadvantages poor countries, therefore, well-off countries owe them rectification.

Each of these claims could mandate serious economic redistribution, including contributions to the public health infrastructures of poor countries.

Discussions of justice require determining what constitutes the “group” or “community” to whom benefits are owed, which is not always easy to achieve. Further, what is owed? At the micro level this might include reasonable availability of drugs successfully developed in the trials or fair benefits of some kind. At the macro level, justice might require that the research is responsive to the health priorities of the host country. Finally, who bears the burden of the duty—governments, drug companies, or non-governmental organizations?

The downside of nesting research ethics within larger theories of global justice is that it could prevent mutually beneficial and consensual agreements between researchers and potential subjects. An example is the planned Surfaxin trial. The parents of children suffering from respiratory distress syndrome in Peru would no doubt want their children to participate in such a trial, even if it included a placebo control. Instead the research was not conducted because of concerns about justice.

Dr. Piot focused on another set of questions:

- What are the challenges particular to doing research in developing countries?

Dr. Piot noted that there can be challenges of injustice within middle- and high-income countries as well as in developing countries. Nevertheless, developing country research can face certain unique obstacles. The first involves historical legacy, that is, the collective memory of communities can be extremely strong based on a history of distrust, rumors, beliefs, and a perception of scientific imperialism.

Second, legislation and standards differ worldwide, which is particularly challenging for multi-site studies, when it can be unclear which standards to adopt or where or how to receive ethics review and approval. Some countries do not have the infrastructure for ethics review, or their review bodies are over loaded, undertrained, or less than independent. Within countries, ethics review bodies might not consistently interpret standards, or they might overzealously interpret protections, never finding the right balance in risk/benefit determinations. In countries with centralized national review as well as local review, there can be disagreements about what is acceptable. This recently has been the case in studies of human papilloma virus vaccines in India, which have been stopped.

The consent process raises challenges to language and custom. Some terms do not exist in all languages (e.g., research, risks) and the need in some cultures to seek permission from others before participating in research has to be recognized. Obtaining and storing human biological tissues also raise ethical questions, with some societies refusing terms under which samples are shared with industry. Restricted export of human tissue by some governments limits research outcomes and impact. Some policies require that study samples be destroyed once the research is completed.

Another set of challenges rises out of poverty and incentives for people to participate—for example, to gain access to healthcare they might not otherwise receive. This is particularly difficult when not doing the research would deny some people access to lifesaving care.

Other challenges are worth noting. Increasingly debates are being waged over intellectual property rights; for example, do study subjects have any claim on intellectual property derived from a study? And, long-term responsibility of investigators and sponsors after a study is complete is an ongoing challenge, not only in terms of mutual benefit but also for study legacy and whether the community will welcome future studies.

Dr. Piot concluded by saying that every international study has ethical and political dimensions, which are not always recognized by researchers intent on answering scientific questions.

Discussion

The debate about whether U.S.-sponsored research has to be responsive to needs “on the ground” raises questions about what is meant by “responsive” and what it means in local contexts. Current U.S. regulations do not address the issue of responsiveness. However, in general, National Institutes of Health (NIH) funded research tends to be responsive to local health needs.

Should responsiveness be a condition for research conducted in other countries? If it were, would it eliminate a false distinction between reasonable availability and fair benefits, because if studies had to be responsive to local health needs, those considerations would be inherent—determinations of benefits could not be amorphous, they would have to be specific. Further, the concept of responsiveness would have to be included in study design as well as potential benefits during and after the study.

Of note, concerns about the Guatemala experiments that brought this panel into existence had little to do with responsiveness; rather, the ethical concerns focus on the treatment of subjects in the trials. In addition, subjects might be very isolated from the larger environment of justice in their country—another reason why responsiveness is not always the principle concern. Concerns about ethical research can be divorced from those about global justice. The first consideration is whether subjects are being treated ethically. If not, no other questions need be asked. If they are, then other questions, such as responsiveness to community needs and global justice, pertain.

It is important to add that some research is conducted in developing countries in an effort to find ways to raise the general welfare of the host community—for example by answering contextual questions about diagnosis and treatment that reduce injustices and disparities—thereby leveling the playing field. In addition, some studies have to be conducted elsewhere because of the incidence or prevalence of a condition—that is, there are scientific justifications. Thus, deciding where studies are done and who will be included involve ethical issues that predate considerations of whether subjects are being treated ethically once a trial begins.

The question was posed, Should U.S. federally funded research be conducted only if justice will be furthered in those countries? Should that requirement be extended to privately funded research as well?

This prompted discussion of whether economic betterment can be included in considerations of responsiveness. It also raised concerns about whether such a stringent standard would eliminate opportunities for potential benefits to individuals participating in research.

The Tuskegee studies are an example of one unethical study that made a segment of the American population very leery of participating in medical research, to this day. Thus, first and foremost, people must be assured that the subjects of research will be treated ethically. That is necessary, if not always sufficient.

Requiring that the research is responsive and attentive to issues of justice could be unacceptable to private interests; thus, would such a requirement be unenforceable? Should such principles be embodied in the form of moral guidance and ethical standards rather than requirements? There was general agreement that no new rules are needed.

Other conditions for the ethical conduct of research in other countries pertain to transparency and a system of oversight. It might be that some sites are not suitable for research because these conditions cannot be met. In addition, sanctions should be in place for investigators and institutions that do not adhere to ethical standards as well as requirements.

Implementation of existing standards, which often are fairly comprehensive, can be the biggest challenge to international research. The highest goals of bringing relief to a population, responding to their health needs, selecting appropriate sites, and designing research can be undermined if standards and regulations are not implemented or monitored, especially for multi-site studies in which some sites are remotely located.

Sometimes economic considerations are perceived to be more important than global justice issues. This can be the case in biobanking, where the host country providing the samples might never enjoy the economic benefits that emerge from their use.

With regard to the Guatemala experiments, subjects were chosen for expediency, not because the research could potentially benefit them, or people like them. They were vulnerable—children, mental hospital patients, prisoners, and prostitutes. Current standards require that if research is to be performed on vulnerable groups, there has to be some promise of benefit to that population, as a whole.

The requirement of informed consent is intended to ensure that subjects understand the risks of participating as well as the potential benefits so they can weigh for themselves whether to participate. Again, that standard was not met in the Guatemala experiments.

It is important to recognize that standards of care are constantly evolving. When AZT was first being tested in African trials, few citizens had access to antiretroviral drugs as the standard of care. Today that is not the case. Yet had investigators delayed research in parts of Africa because the standard of care was not universally state-of-the-art, many more people would have suffered as a result of delays in the research.

Some would argue that research with a proven therapy should not be conducted in populations where that therapy is not available, because the research could just as easily be done elsewhere where the treatment is available. The response to that is that some research has to be conducted on location because the background conditions are different (e.g., infrastructure, resources), which can affect the effectiveness of the treatment.

Session 2: Respecting Diversity and Community Engagement

Nandini K. Kumar, M.B.B.S., D.C.P., M.H.Sc., COL Nelson Michael, M.D., Ph.D., and Dirceu Bartolomeu Greco, M.D., Ph.D.

Questions posed to the panel included:

- How can one concretely demonstrate respect for transnational standards and other countries' standards for human subjects protection?
- How can one demonstrate respect for local cultures?
- What good participatory practices would ensure meaningful community engagement in research activities?

Dr. Kumar began by noting that not only are there north/south cultural differences, but also east/west differences. These can be cultural, socioeconomic, political, or even genetic. Even within a country like India, there are vast cultural differences as well as variation in the relative influence of the central versus state government. These variations are compounded by differences in the capacity to oversee human subjects research, with some regions doing a better job than others and many unevenly applying the requirements. Layered on this is the multitude of standards to which research might be subject (e.g., ICH-GCP, WHO, CIOMS, government regulations).

Dr. Kumar mentioned the problems that can arise in regions that discriminate against females. For example, in some communities “consent” for females to participate is provided by others (not parents or legal guardians). Other cultural values can interfere with study designs; for example, despite advanced planning, a polio vaccine program ran into problems in a particular community that would not allow males to be vaccinated because they believed it would make them sterile. Examples such as this highlight the need to prepare a site in advance.

One issue that is being debated right now in India is compensation for research-related injury, which, according to the directive of the Drugs Controller General, bioethics committees have to ensure is paid for by sponsors—governments or non-governmental organizations. In addition, when research is conducted in poor populations, what may be considered inducement is a concern, even for something as simple as providing a meal for participants coming from difficult and far-off terrains for a follow-up.

Dr. Michael described his involvement in HIV vaccine studies in Africa and Thailand, emphasizing the importance of ensuring community engagement from the local community level on up. Although the HIV research community has led the way in community engagement, it does so unevenly.

Guidance in this area comes from the *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*, issued by UNAIDS and AVAC in 2011. These guidelines focus on identifying the stakeholders, then adhering to principles such as respect, mutual understanding, integrity, transparency, accountability, and stakeholder autonomy. Specific stakeholder engagement activities are then suggested, for example, forming stakeholder advisory mechanisms, selecting sites, developing communications plans, and planning for post-trial access.

It is critical to recognize that the trial participant sits within a sphere of stakeholder communities, starting with family and friends at the closest level, and moving through the community to the

non-governmental organizations conducting and sponsoring the research, to regulatory bodies and national governments. An important path to partnership lies in the formation of a community advisory board, which can link the research team and the stakeholders in an inclusive manner. The board should be viewed as a way for the community to speak to the external stakeholders in the sphere, not necessarily always the other way around. Such boards can serve as important bi-directional means of communication before, during, and after the trial.

Dr. Greco concluded the presentations in this session by citing CIOMS 2002 *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Guideline 10:

Before undertaking research in a population or community with limited resources, the sponsor and the researcher must make every effort to ensure that:

- the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
- any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.

UNAIDS/WHO has also issued guidance, *Ethical Considerations in Biomedical HIV Prevention Trials* (2007), which list circumstances in which such trials should not be conducted, for example, when the product to be tested would not be appropriate for use (should it be proven safe and effective) in the community that would participate, or when the capacity to conduct independent and competent scientific and ethical review does not exist. Other reasons for not conducting research include the inability to obtain voluntary informed consent; when conditions affecting potential vulnerability or exploitation are so severe that risks outweigh benefits to that population; when local laws and regulations are unknown or legal barriers exist; when agreements have not been reached among stakeholders about standards of prevention or access to care and treatment; or when agreements have not been reached about post-trial access. Conditions for scientific and ethical review are provided as is specific guidance regarding vulnerable populations.

Dr. Greco cited another WHO document, *Guidance on Ethics of Tuberculosis Prevention, Care and Control* (2010), which emphasizes many of the same issues as the WHO/AIDS documents, including the principle that “international research should be conducted in a manner that ultimately helps low- and middle-income countries develop the capacity to do research themselves.”

Dr. Greco concluded with the following:

1. It is crucial to develop universally acceptable ethical principles, considering all culturally relevant approaches for the implementation of research projects.
2. All researchers, both from developed and developing countries, should collaborate during all stages of the study, from the development of the protocol until the application of the results.
3. Decisions about post-trial access to efficacious products should be based on the principle of justice. Volunteers should have access to drugs, vaccines, interventions, prevention strategies and any other benefits resulting from the study.

4. Financing of studies should include funds for strengthening local capacities, not only those related to the aims of the project, but also for local infrastructure, and to boost the developing country's capacity to conduct research projects.
5. Inclusion of vulnerable individuals shall warrant special justification and appropriate protection and should occur only when the project objective is for their benefit.

Discussion

Although there might be disagreement over which standards are the best, there is tremendous overlap among them. What is relatively new is the focus on community engagement, as led primarily by the HIV research community. Of note, community engagement was not immediately embraced by the research community, but it has now become the norm.

True community engagement provides opportunities for ongoing oversight and monitoring of the research activities. While this might not alter the scientific approach, it is an important political consideration because it allows communities to protect themselves and become invested in the ethical and valid conduct of the research. The need for community engagement has more ethical salience when there are low levels of trust or greater power differentials between those conducting or sponsoring the research and the community.

Community engagement involves: 1) identifying the community, 2) identifying the gatekeepers, and 3) understanding who speaks legitimately for the community. This is not always possible or easy. And, some local interests will block research, even if it comes at the expense of the research or potential benefit to those who participate. Thus, it is important to not overly idealize the concept of community engagement. Moreover, buy-in at all levels of stakeholders is unlikely to happen all of the time. Yet community engagement should remain an aspirational principle. It is necessary, but not sufficient, to protect a community from research harms. However, some efforts at engagement might be successful in terms of engagement but result in the research not being conducted. That should not necessarily be considered a failure.

Investigators also should be mindful of not arriving in a community with the study design and methodology pre-packaged and immune from modifications based on community input.

The longer research teams are involved in communities, the easier the process becomes, as mutual respect and trust develop. In addition, Internet access has changed the dynamic so that no researcher is really isolated or far from view of community (and outside) critics and scrutiny.

Several justifications can be made for community engagement. First, the potential benefits to be gained from the research would extend to the entire community, not just the individual subjects. Second, it can reinforce the normative guidelines issued from higher authorities. Third, it can form a critical communication and information dissemination mechanism for the research team. Fourth, it allows a community to determine how it will use its local resources (including human resources). Fifth, it can improve the study design.

Who speaks for potential research subjects is an important consideration. In some societies, women cannot participate in research without their husbands' consent. While that is troubling to

some, more troubling are situations where women do not want to participate, but their husbands (or fathers or other male authority figures) say they must. In these cases, it is incumbent on the researcher to find a way for women to say no without endangering their status in the family or community.

The greatest challenges in respecting diversity and community engagement emerge when researchers want to enforce different standards than exist on the ground.

The discussion ended on the issue of defining equivalent protections. On the one hand there are substantive standards that can be judged for their equivalency, for example, the requirement for independent ethics review. Then there are procedural standards, for example, obtaining written informed consent or keeping minutes of ethics review meetings. It would be considered a sign of respect for the U.S. Government to recognize equivalent protections in other countries, particularly with regard to procedural requirements that reflect local standards and norms.

Session 3: Seeking Unity and/or Harmonization – Transnational Standards and Universal Principles

Sergio Litewka, M.D., M.P.H. and Huanming Yang, Ph.D.

The following questions were posed for consideration:

- Is it necessary to redefine a universal framework for bioethics, while leaving countries some freedom to work within it?
- How can one raise basic minimum standards for human subjects protection to avoid “forum shopping” for research?
- Are current transnational standards insufficient in some way? Are any transnational standards out of date?
- Is it necessary to have another joint transnational standard for human subjects protection?
- Is there a need for an international structure to issue interpretations or guidance on the implementation of common standards and/or principles?

Dr. Litewka said that it is not the norms that are in question but rather their enforcement. Existing standards and norms, in general, are similar, and no more are needed. Although guidelines are useful, the challenge still lies in how to transition from aspirational to procedural norms. Cultural differences can be addressed as long as there is respect.

To improve implementation, education is needed for investigators and ethics board members. There should be singular standards for ethics training because the standards are so similar. What is needed is a critical mass of people who understand the ethical standards. It is vitally important that capacity for ethics review and oversight be built in and by countries where it does not exist. There are minimal standards on which all can agree, and those should be well understood internationally. These include the need for independent review, informed consent, and a favorable risk/benefit ratio.

Dr. Yang said that it is not so important where the standards came from—there is a great deal of “horizontal” compatibility there. What is more of a challenge is the vertical integration of these

standards, that is, in a given locale, how are they being implemented at the local level? He noted that since the end of the Cold War, several countries have entered the discussion of research ethics that were not there before. Of note, several international documents, such as the Declaration of Helsinki, have undergone several revisions. We should be asking which standards are still relevant, and which need to be reconsidered as issues have changed over time.

Some countries look at the U.S. or international standards and question whether U.S. or European or Japanese investigators themselves are adhering to their own standards. In some ways, that question must be addressed before looking elsewhere for transgressions. From his perspective, Dr. Yang said people look to the United States to set the highest standard. However, just because a study meets U.S. or international standards does not mean that host countries also should give them their stamp of approval.

Discussion

There is convergence on most ethical standards. Where there is divergence is in how they are implemented region by region, or country by country.

One question to consider is the legitimacy of the standards. In political theory, one makes a distinction between the substantive justice of standards—are these good standards, are they correct norms—and the provenance of those standards or norms. Are they viewed as legitimate, that is, coming from the right kind of place or the right kind of people? Is it likely that standards and norms that have been developed through a broader deliberative process have greater legitimacy than those drawn up by a smaller and more closed group of people? It is worth noting that the United Nations and the World Health Organization tend to be dominated by the same group of countries.

Although there was little enthusiasm for certification programs, the concept of developing international standards, such as ISO, was raised.

While capacity building is important, investigators and sponsors should be sensitive to the perception that they might be coming into the host country merely to “teach them what they want done.” In addition, it is important to recognize that in some countries ideological issues might prevail. For example, opponents might not be as concerned about the nature of the research as they are about the funder of the research. Moreover, investigators should not assume that a host community wants capacity built—they should be asked and invited to do so.

More transparency and accountability will help ferret out ethical breeches that have managed to get past ethics review and community-based oversight. Public scrutiny is an added safeguard. In the United States, ClinicalTrials.gov was a step toward greater transparency and scrutiny, although it does not capture all human subjects research. One reason for not requiring that all research be entered into the current database is the burden, especially for studies involving few subjects and less than minimal risk. There are also concerns about how the public might use results that have not yet been vetted through peer review.

The panel arrived at consensus surrounding the idea that:

To enhance transparency and accountability, the United States should consider requiring all research that involves greater than minimal risk to subjects to be registered and results reported.

However, it was noted that while transparency is necessary, it is not sufficient. It was added that among the best protections for participant health and well-being is the conscience of a well-informed scientist. This can be aided by an activist community that benefits from the ability to use social networks and the Internet as part of the monitoring capacity.

Session 4: Regulatory Reach, Compliance, and Enforcement

Christine Grady, R.N., Ph.D. and Luis López Dávila, M.D.

- Once guidelines and regulations are designed/developed, how can one ensure that they are effective?

Dr. Grady presented the views of Julius Ecuru, which were submitted in writing, as well as her own.

In response to this question Mr. Ecuru said that effectiveness of guidelines depends a lot on the process by which they were formulated. Those that are formulated in a transparent and participatory manner are more likely to be effectively implemented. However, once guidelines and regulations are developed, they should be immediately institutionalized, for example, by formally launching them in a public event, publishing and widely disseminating them, and putting in place infrastructure to support their implementation. The next step would be to immediately roll out a training program on their interpretation and use a monitoring framework to collect feedback. Effective implementation of guidelines in Uganda relies on forums or interactions and networking among the stakeholders.

Dr. Grady's own view is that the interpretation of guidelines must be continuously revisited and updated, and efforts made to ensure that investigators and IRBs are aware of them, which is not always the case. In the United States, the concept of research ethics consultations is spreading, which can provide a forum for discussion of some of the more complicated issues people encounter in research. Typically, consultants are called in to assist investigators with addressing ethical concerns (e.g., study design, standard of care) before the proposal even goes before an IRB.

- How can individuals/organizations other than investigators contribute to improving systems for human subjects protection?

Mr. Ecuru considers individual groups and organizations to be part of the research community, who share the same goal of improving the protection of human subjects. It is, therefore, absolutely essentially that individuals, groups, and communities appreciate the value of ethical research. They should be the first custodians of enforcing the regulations and should support research ethics training. They are the eyes on the ground to report any non-compliance.

Dr. Grady added that no investigator is working alone; he or she is typically part of a large team, all of whom should be trained in research ethics and responsibility. They should embrace a culture of responsibility, not just compliance with a system of checking off boxes.

- How can one improve compliance monitoring, for example monitoring of IRBs and ethics review committees (ERCs)?

Mr. Ecuru submits that compliance monitoring can be improved by encouraging investigators to undertake their own self-monitoring. Further, ethics boards must have standard operating procedures for monitoring, which must be a requirement for accreditation. The IRB's host institution should also have a role in ensuring that the IRB is performing according to standards. He recommends accreditation as a standard.

Dr. Grady added that accreditation will only work if the process measures outcomes. The current accreditation system in the United States focuses only on standard operating procedures and documentation. It is overly focused on compliance and documentation.

- What mechanisms promote enforcement of human subjects protection?

Mr. Ecuru wrote that to promote human subjects protection we must balance education with regulation. Education of both investigators and the research community helps to instill good ethical values and behavior, thus promoting ethical conduct. Education can be done in a variety of ways. Journal policies requiring evidence of ethics approval have encouraged compliance, especially in countries where enforcement of regulations is weak.

Dr. Grady added that we need to find a way to understand whether IRB deliberations and efforts reflect the best effort. A written justification of deliberations and decisions involving particularly complex ethical dilemmas would be useful. To promote a culture of responsibility, we might need coaches and mentors in addition to training. Perhaps there should be remediation for those who have made mistakes.

Dr. López closed the session by focusing on how to improve compliance monitoring and on mechanisms to promote enforcement of human subjects protection.

It is important to consider context, for example, whether vulnerable populations are involved because of economic, social, ethnic, linguistic, or other reasons. Other contextual factors include the prevailing health system and who is covered, local and regional regulations, available infrastructure, the oversight system, research practice (e.g., design, problem studied, impact on the country or community, publications, dissemination of local knowledge), and practical ethics (e.g., training, accreditation). Whether federal funds are used for the research also influences monitoring and enforcement.

Based on these considerations, one could construct a “vulnerability map” for classifying countries, which would assist in selecting sites for research and determining oversight and enforcement strategies.

Dr. López suggested the following courses of action for monitoring and enforcement:

- Create a system at the regional level for monitoring and auditing IRBs and ERCs, strengthened in countries with greater vulnerability;
- Promote local governance of institutions related to research
- Promote support networks in ethics research;
- Create a Web Portal: open protocol (summary), highlight ethical issues, budget, human resources;
- Reward innovative strategies for projects that reduce the gap between protection of research subjects; and
- Sanction offenders, including IRBs, ERCs, researchers, and institutions.

Discussion

In encouraging a culture of responsibility, the goal is to move away from a system of compliance only and toward one of ethical reflection. One obvious way to promote such a culture is through education and training. The need for such reflection is all the more important in an environment where researchers have come to view the regulatory requirements as unnecessarily burdensome, especially when they do not appear to improve human subjects protections.

Creating a vulnerability map raises the question of who would do so. If one were to exist, it could be used not only to select sites for research, but also to identify countries or regions in need of capacity building. Because researchers and institutions are interested in capacity building, it is an area where interests and incentives would be well aligned.

One case that illustrates some of the issues raised during the discussion involved early studies in Africa of heterosexual transmission of HIV. Dr. Piot described the challenges. The local ethics board was comprised of professors at the university; thus, the UNAIDS team felt that an independent review body was lacking. Efforts to bring in outside reviewers were viewed as: 1) questioning the judgment of local leaders, and 2) “buying” an ethics board that would approve the protocol. Other issues that emerged centered on continuing care for those infected during prevention trials, the responsibility of funders, the appropriate comparator arm, and determining the standard of care. The research team could never get consensus on many of these issues and the discussions were often emotional and ideological. In such cases, it is sometimes easy to take shortcuts or abandon the research altogether. The development of guidelines for community engagement in such studies has helped pave the way. Such engagement provides researchers with the assurance that not only do they think what they are doing is right, but others do as well. However, even an ethically designed and conducted study is likely to still draw controversy and opposition. We might have to tolerate different decisions and outcomes even for well-designed and executed studies.

If capacity building becomes a principle or standard for conducting research in resource-poor countries, then the funds must be available for doing so. NIH provides substantial overhead to U.S. institutions for infrastructure, but does not provide the same level of resources for research conducted abroad.

The panel arrived at the following conclusion:

Open and inclusive dialogue is crucial to showing respect to communities, learning about context, responding to concerns, and working toward effective capacity building.

In some cases, there might be disagreements among scientists about the most scientifically sound or justified approach especially concerning study design and use of comparator arms. However, determinations of what constitutes good science, or “good enough” science, are also ethical decisions. This is an important message for those who separate ethics and science as if there was a distinct line between them.

Session 5: Roundtable and Discussion

Panel members were encouraged to offer conclusions and recommendations based on the discussions. They discussed various ideas, including:

- **No new rules are needed. Rather, greater efforts are needed to implement existing rules and make the process more transparent. Transparency can include registration of trials, publication of negative results, issuance of practice guidelines, or certification programs, as examples. Within the United States, harmonization of existing rules would add clarity to the oversight process.**
- **Experimentation is needed to explore the best means for creating a culture of responsibility. Existing training approaches (e.g., Web-based, self-paced study) do not appear to be accomplishing that goal. In addition, best practices in ethics review can help instruct others on what a culture of responsibility looks like in practice.**
- **Promoting a culture of responsibility includes making a commitment to capacity building.**
- **Researchers and the ethics community should be more proactive in anticipating issues that might arise with new technologies or research strategies. “Preventive ethics” can anticipate and address some challenges before they emerge.**
- **The U.S. Government must find a way to recognize equivalent protections.**

Closing Remarks

Dr. Gutmann suggested that the panel consider and analyze two case studies of contemporary research that illustrate good models for international studies in order to highlight best practices, for example, transparency, accountability, community engagement, appropriately trained researchers and ethics reviewers. Staff will work with the panel to identify two cases for discussion at the next meeting.

The panel will convene again July 27, 2011, in Washington, D.C.

The work of the panel will be published as proceedings of each of the three meetings, accompanied by a summary that provides an overview of the panel's discussions, conclusions, and recommendations.

Meeting Three
July 24, 2011
St. Regis Hotel
Washington, D.C.

Members Present

Amy Gutmann, Ph.D., Chair
John D. Arras, Ph.D.
Julius Ecuru, B.Sc., M.Sc., Dip.IRE.
Christine Grady, R.N., Ph.D.
Nandini K. Kumar, M.B.B.S., D.C.P.,
M.H.Sc.
Sergio Litewka, M.D., M.P.H.
Luis López Dávila, M.D.

Adel A. F. Mahmoud, M.D., Ph.D.
COL Nelson Michael, M.D., Ph.D.
Peter Piot, M.D., Ph.D.
Huanming Yang, Ph.D.
Boris Yudin, Ph.D.

Members Absent

Dirceu Bartolomeu Greco, M.D., Ph.D.
Unni Karunakara, M.B., B.S., Dr.PH.

Opening Remarks

Dr. Gutmann, Chair, Presidential Commission for the Study of Bioethical Issues (the Commission), opened the meeting and asked panelists and staff to introduce themselves. She once again reminded the panel of the two overarching questions that President Obama has asked the Commission to answer: 1) to what extent do current rules and practices in U.S. Government sponsored international research protect people from harm or unethical treatment; and 2) what, if anything is needed to improve those rules and practices? Dr. Gutmann added that the London meeting helped crystallize several key concepts as critical to human research protections internationally, for example, distributive justice, respecting diversity, the need for community engagement, the status and implementation of transnational standards, universal principles and variations, regulatory reach and enforcement, and the importance of not creating additional unnecessary regulations.

Session 1: Review of Draft Findings and Recommendations

Dr. Gutmann briefly reviewed the draft findings and recommendations that were developed following the June meeting of the panel. She stated that the goal of this meeting was to discuss two case studies that are illustrative of central issues in international research—and that can inform the panel’s recommendations—and to come to consensus on the findings and recommendations so that they can be forwarded to the full Commission for consideration.

Panel members were asked to consider whether anything was missing from the draft findings and recommendations and for general reactions to the draft before them. It was noted that since the June meeting, the Department of Health and Human Services announced that the federal government is considering various ways of enhancing the regulations overseeing research on human subjects. Before making changes to the regulations, the government is seeking the public’s input on an array of issues related to the ethics, safety, and oversight of human research. Given this development, as well as the previous discussions of the panel, it was determined that the first draft finding of the panel, “no new rules are needed,” was too strong and should be

modified. Instead, they proposed a recommendation stating something to the effect that while no new rules are needed, existing rules should be revisited, harmonized, and possibly revised.

An additional issue to be considered in the recommendations is expressing the need for an ongoing international dialogue on human subjects protections. The work of this panel should be considered the beginning of a process, not its conclusion. Panelists raised questions about who would be responsible for enacting the recommendations should they be adopted, and emphasized the need to address concerns about how and whether existing regulations are being implemented, tracked, and enforced. Special concerns arise in countries where no regulations are in place or the existing regulations are not supported by adequate infrastructure. Finally, panel members proposed that they should consider whether the recommendations should extend beyond research that is conducted or supported by the U.S. Government.

Detailed discussion of the draft findings and recommendations was scheduled for the afternoon session.

At the June meeting, Dr. Gutmann suggested that the panel consider and analyze contemporary case studies that illustrate good or controversial models for international research in order to highlight best practices, for example, transparency, accountability, community engagement, and appropriately trained researchers and ethics reviewers. The morning sessions focused on discussing the two case studies selected for discussion. Questions for consideration included:

- What makes this an example of “good” research?
- What controversial issues arose in this case?
- How does this case model best practices?
- How does this case reflect and/or inform the Panel’s findings/recommendations?

Session 2: Case Study #1- RV144 Phase 3 HIV Vaccine Trial in Thailand¹⁶

COL Nelson Michael, M.D., Ph.D.

Dr. Michael described the goals of a randomized, double-blinded, placebo-controlled Phase 3 trial of Sanofi Pasteur live recombinant ALVAC-HIV clinical trial priming with VaxGen gp120 B/E boosting in HIV uninfected Thai women and men with heterosexual risk for HIV infection. The study sought to determine whether the prime-boost vaccine combination (also referred to as RV144) was safe and effective at reducing rates of HIV infection or reducing viral load in vaccine recipients who became HIV infected over the course of the study. The study was co-funded by the National Institutes of Health and the U.S. Army and involved U.S. and Thai scientists. RV144 was the first HIV vaccine shown to be effective at reducing the risk HIV infection with an efficacy of 31.2 percent measured 42 months after enrollment.¹⁷

Dr. Michael said that the study was controversial because previous efficacy trials using the VaxGen gp120 B/E component alone were not found to be effective in men who have sex with men in the U.S. and Thai injection drug users. The ALVAC-HIV component, while never tested in an HIV vaccine efficacy trial before, generated immune responses in humans that were generally considered weak. The size and cost of the RV144 trial drew criticism because many members of the scientific community were skeptical about its chance for success and thought

that the resources devoted to this study would be better spent supporting HIV basic research grants to academia. Proponents of the trial argued that since essentially nothing was known about what immune responses would be needed to protect against HIV infection, a phase IIB efficacy study was the only way to gain insight into the utility of the RV144 prime-boost combination.

The study, which included more than 16,000 subjects, involved a series of injections and booster shots over a period of six months. It took six years to complete (2003-2009). Dr. Michael said that there was high enthusiasm in Thailand for the study and the Thai government was very involved in the process inclusive of the Prime Minister. The Thai Ministry of Public Health preferred a top down approach to community engagement, which limited the effectiveness and practice of this engagement compared to contemporaneous HIV clinical research studies, said Dr. Michael. The Ministry of Public Health felt very strongly that they should release the results of the study to the RV144 volunteers two weeks after the study results were known and before the study had undergone peer review for publication in the *New England Journal of Medicine*. This proved to be very challenging when statistical criticisms of the study ensued and the study team could not openly debate the merits of these criticisms while the study was under review for publication. This caused increased confusion in the community that was only resolved when the study was published simultaneous with presentation at an international scientific conference four weeks following the news conference.

Much care was taken by the trial partners to negotiate access agreements to the vaccine components based on levels of efficacy that might result from the study. These negotiations involved the vaccine manufacturers and the Government of Thailand in partnership with the U.S. Army (the trial Sponsor) and the NIH (the majority funder of the study). Access to the vaccine components for use outside of Thailand would have required separate negotiations. The World Health Organization/UNAIDS, the Asia Vaccine Advisory Network, the Thai AIDS Vaccine Evaluation Group, and the AIDS Vaccine Advocacy Coalition all provided input into the study from its inception through interpretation of its results and deliberations about next steps. All major decisions for RV144 were vetted by the U.S. Embassy in Thailand and the Thai Ministry of Foreign Affairs.

IRB approved stopping rules were in place throughout the study that would be triggered by an independent Data Safety and Monitoring Board for evidence of harm to volunteers, exceptional levels of efficacy, or evidence for study operational futility—none of which occurred in RV144. Rules were mutually agreed upon by the Ministry of Public Health and the other study partners for providing placebo arm participants with access to the vaccine should efficacy exceed 50 percent. However, if the efficacy had exceeded 50 percent, there would not have been sufficient vaccine available to provide access to others for nearly two years owing the reluctance of the trial partners to develop a large stockpile of vaccine whose promise was predicted by many to be low. This would likely have raised controversy in Thailand and the global community but since efficacy was 31.2 percent, this was never an issue.

Discussion

It was generally agreed that the trial was scientifically valid despite criticisms at its onset. HIV infection was a critical public health problem in Thailand and prior vaccine studies had failed to

provide insight on the best approach going forward. Thus, there was a genuine scientific question that many felt was worth exploring despite others feeling that it was not an appropriate use of research resources and it was perhaps not worth exposing subjects to risk of harm. While the trial generated significant controversy and discussion in the scientific community, it demonstrated for the first time that an HIV vaccine could reduce HIV infection risk.

Concern was raised about modifications made to the study midstream and whether they could have significantly changed the endpoints. Further discussion revealed that all such changes were both IRB approved and were made prior to the final study data file being closed for blinded statistical analysis. In addition, concern was raised that the confidence intervals surrounding the vaccine efficacy result were larger than would be acceptable in many industrial studies seeking FDA approval, but further discussion emphasized that RV144 was a proof of concept study and not viewed by the FDA from the start of the trial as a pivotal licensure study. Further studies exploring the RV144 prime-boost approach are planned to build on the initial results. Taken together, these concerns highlight that study design and statistical methods have ethical relevance—a reality that is not always fully recognized when considering the ethics of a study.

The study also raises questions about transparency and the appropriate time at which to publicize clinical trial results. That the Thai government preferred to report results before they had been exposed to the peer-review publication process generated controversy in the scientific community. Panel members agreed that reporting initial clinical trial results too soon is problematic, but preferable to never reporting them or concealing them, as was the case in the Guatemala studies.

Thailand was considered a reasonable place to conduct the study because it had a strong commitment to public health, a national HIV vaccine plan, stringent requirements for research oversight, a social structure in which to conduct the study, and a growing HIV problem. In addition, the Thai government requires that research conducted within its borders hold out the promise of benefit for the Thai population. This highlights the need for U.S. researchers to assess foreign standards against U.S. standards. They should determine which standards are more stringent and/or which should prevail.

This trial illustrates one version of community engagement, in which the process was viewed by the Thai Ministry of Public Health as a largely unidirectional method of pushing information out from the Ministry to the community rather than a bidirectional communication framework. Furthermore, it highlights the need for continuous, inclusive, and transparent deliberation between clinical trial partners and governments to strike the appropriate balance between individual views and international normative body guidelines for trial execution. Being responsive to host nation governments is necessary in international research but it is not sufficient alone to ensure the protection of clinical research subjects.

Session 3: Case Study #2 – Randomized Control Trial of Adjuvant Treatment for Breast Cancer in Vietnam¹⁸

Adel Mahmoud, M.D., Ph.D.

Dr. Mahmoud described this study, which was originally proposed in 1992 by Richard Love, a cancer researcher at the University of Wisconsin, Madison. Love was proposing to conduct a randomized controlled trial for adjuvant therapy of breast cancer in the Socialist Republic of Vietnam. At the time, standard therapy for treating breast cancer in the United States included surgery plus an adjuvant, such as radiation therapy, chemotherapy, or hormonal therapy, or some combination of these treatments. The effectiveness of hormonal therapy as compared to other adjuvants was not well understood.

Most women in Vietnam did not have routine access to adjuvant therapy. Thus, Dr. Love wanted to determine whether use of hormonal therapy as an adjuvant yielded better outcomes than surgery alone (which some would say was the standard of care in Vietnam at the time). The study could not be conducted in the United States because adjuvant therapy (primarily chemotherapy) was the standard of care; thus, a control arm that did not include an adjuvant was considered unacceptable. The proposal ran into several obstacles when it was reviewed by the university IRB, which resulted in several modifications to the study design.

The first issue flagged by the IRB focused on determining the standard of care given local circumstances. An argument could be made that even though use of adjuvant was the widely regarded superior treatment, lack of access to an adjuvant, especially chemotherapy or radiation therapy, had to be considered in trying to determine the best course of care in Vietnam. Some reviewers of the initial study said that not providing the highest standard of care (the U.S. standard) resulted in exploitation of economically disadvantaged Vietnamese women. In response to these criticisms, the design was modified to allow women to cross over to the study arm from the control arm if their cancer recurred.

Second, Love suggested that getting informed consent from the study participants was not possible because of language barriers, a paternalistic culture, and the challenges of explaining the concepts of randomization and control arms. He proposed using surrogates in the consent process, specifically educated, American-living Vietnamese immigrants or directors of the Vietnamese Women's Union. He visited Vietnam to assess the feasibility and acceptability of relying on a surrogate consent process, which he reported as a viable option. The IRB rejected that proposal and required individual informed consent, documented with a signature.

Thus, this case study raises several issues: determining the standard of care when developing a randomized controlled study in a country where the local standard of care is below the standard of care found in the United States (or country of the investigator); whether surrogate consent is ever acceptable and under what circumstances; and what form consent should take given local customs and preferences. It also emphasizes the importance of independent ethics review as a means to enforcing standards.

Discussion

A central issue in this case study is the use of a no-adjuvant treatment control arm, which the researchers proposed was in line with the standard of care in Vietnam at the time. A related issue is whether those in the control arm would benefit from receiving care (more careful follow-up and treatment for recurrence of cancer) to which they might otherwise not have access—thus, it

could be considered a benefit of participating. In some cases, standards of care can be determined based on written guidelines or recommendations. However, since standards are not always available or uniform (for multi-country studies), researchers and IRB members sometimes have to make judgments about the standard of care based on local public health needs and priorities and the availability of scarce resources. In any event, if research is justified purely on the ground that it provides humanitarian care, poor science may result. It is, however, sometimes acceptable—even laudable—to search for an intervention that might have the potential to work just as well somewhere else, but at less cost. Sometimes such studies require more than two experimental arms, and appropriate statistical analyses can help provide justification for proceeding under such circumstances.

Discussion focused on the fact that the IRB process worked to enforce ethics standards. However, requiring written informed consent might have infringed on local norms or customs or signaled a lack of respect for cultural standards. Although it is essential to obtain voluntary informed consent from individuals, the form of documentation of consent might differ.

Surrogate consent (except for limited circumstances such as emergency research and studies that involve children and decisionally impaired individuals) is a perilous practice, as it opens the door to discrimination and exploitation of more oppressed populations or groups. Thus, the IRB rightfully refused to allow surrogate consent procedures in this case of research with competent adult women.

Panelists agreed that this case demonstrates the value of the IRB process, which if thoughtful and not overly rigid on procedural requirements can improve a study and facilitate answering an important research question. Research conducted in other countries and cultures is essential, and efforts should be made to promote such studies, not derail them.

Session 4: Findings and Recommendations

Adequacy of Existing Rules

The panel agreed that it is important to first recognize that over the past five decades a great deal of progress has been made in the development of rules and standards for the protection of human subjects. The U.S. has not only developed policies that are consistent with international standards and norms, but it has also played a leading role in the development and implementation of rules that have facilitated the advancement of international research and international collaborations. The volume of international research has increased over time, and it is exceedingly important. Thus, it is important to ensure that standards are being enforced internationally. It is also important to recognize that standards and norms are always evolving, as is the clinical research environment, and will continue to change over time, and thus should be periodically assessed for currency.

In addition to the proliferation of rules, transparency of research conduct and oversight has increased. For example, scientific and ethics review provide two means for disclosing research goals to disinterested parties for evaluation. Registration of trials in registries provides for more

openness, and publication of peer-reviewed findings provides a system for weighing and reporting research results.

Although many standards have emerged in recent history, not all international rules are the same, nor are they all harmonized. Nationally enforced rules vary widely across countries, which creates challenges for research sponsored by one country and conducted in another country, or several countries. This is particularly true when rules and standards are in conflict or are more leniently enforced in one country as compared to another. And, when a country does not have any rules, greater disharmony and disparities arise. One negative consequence of expanded international research is the potential for exploitation of populations lacking oversight systems or the financial resources or power to protect themselves from exploitation. With greater economic disparities comes a greater opportunity to exploit people in the lowest income areas. This puts a premium on having standards and procedures in place that protect human subjects of research.

The panel agreed that there is no need for new rules in the United States; however, existing rules need to be revised and harmonized. Where they exist, current rules and guidelines are sufficient to ensure human subjects protections if they are appropriately implemented. Existing standards generally include the same basic protections, for example, independent prior review and informed consent. More guidelines, *per se*, will not help except in those countries without rules in place. In fact, for some research activities in some places, fewer guidelines might be better because the current rules have become overly burdensome and somewhat conflicting from a procedural perspective.

Even uniform rules are interpreted and implemented differently against the complex backdrop of cultural, political, and economic influences. Thus, even when universally agreed upon, principles are not always uniformly applied. This is to be expected in a pluralistic world. One persistent challenge in this complex environment is the tension between substantive and procedural requirements within and across borders. For example, although all standards might contain a substantive requirement for informed consent, how consent is obtained and documented—a procedural matter—might differ. At times, procedural concerns can overtake substantive requirements, which can provide a real barrier to international research.

Determining whether protections in other countries are equivalent to U.S. rules can be challenging, and little clarity is provided in current rules or guidance. Even in cases where protections appear to be substantively equivalent, procedural differences can lead to the conclusion that the protections are not equivalent. For example, although U.K. rules are similar to those in the United States, they are deemed nonequivalent because they do not require annual continuing review by an ethics board.

The panel also discussed the reach of existing rules, that is, whether all investigators should adhere to the rules, regardless of their source of funding. Because international research is often conducted by for-profit industry, it is important that these entities adhere to the same high standards required when public funding is provided.

Promoting Community Engagement

Community engagement, while highly valuable, is not a sufficient guarantee of ethical research. It is not a substitute for individual informed consent, scientific validity, or independent ethics review. It is an additional, supplemental activity that can not only improve and facilitate research by honoring local norms and culture, but also provides opportunities for ongoing oversight and monitoring of research activities. It is an important political and ethical consideration because it provides an opportunity for communities to protect themselves and become invested in the ethical and valid conduct of research. Community engagement can be especially useful when there are low levels of trust or greater power differentials between those conducting or sponsoring the research and the community.

The term “community” can mean many things and defining it is an essential part of the engagement exercise. At a minimum, the community should include those affected by the study itself, that is, patients and healthy volunteers. As appropriate, the community might extend to family and friends, community leaders, local institutions, and government officials and agencies. However, a community group or community representatives might not always be working in the best interest of individuals in the community—a possibility that must be recognized and guarded against.

A recent publication, *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*,¹⁹ provides systematic guidance on the roles and responsibilities of trial sponsors and trial implementers towards participants and their communities. These guidelines provide a useful starting point for all types of clinical research.

Individual Informed Consent is an Essential Protection

Informed consent is an essential element in the protection of clinical research subjects. The panel recognized that current regulations allow a waiver of consent for certain, less-than-minimal risk research studies, and that surrogate consent is permissible in limited circumstances, for example, research involving children, adults with decisional impairments, or conducted in emergency settings. Individual informed consent is necessary but not sufficient to protect research subjects. Because of its necessity, it is important to find the most appropriate procedures for documenting that consent was obtained using a method that is transportable into the future.

The Need for Transparency and Accountability

The panel agreed that, in general, the conduct of clinical research has become a more open and transparent process than it was 50 or 60 years ago. Advances in research review and monitoring, plus technological advances that facilitate more rapid communication and dissemination of research activities have contributed to these changes. Even so, greater efforts are needed to enhance transparency, monitor ongoing research, and hold researchers and institutions responsible and accountable for violations. To enhance transparency and accountability, the governments could consider requiring public registration and results reporting for higher-risk research involving human subjects. Current U.S. federal law requires advance registration and results reporting in a public database (ClinicalTrials.gov) for many, but not all, clinical trials. In addition, many journals require some assurance that ethical standards are adhered to during a research study.

Training Needs

Everyone engaged in human subjects research must be aware of ethical standards and how they are operationalized. This is a requirement for receiving funding from many U.S. federal agencies. However, there are criticisms of the nature of ethics training and whether it is effective. In addition, training is not a requirement for conducting FDA-regulated research that is privately funded. Training should be mandatory for all those conducting clinical research and it should focus not just on the rules but also on their ethical justifications.

Compensation for Research-Related Injury

In many countries, researchers must carry insurance to cover compensation to subjects harmed as a result of research. In the United States, some institutions carry liability insurance, but it is not a requirement for receipt of federal funds for research. Subjects who are harmed have legal recourse, as consent forms are not permitted to contain exculpatory language. But compensation is generally limited to negligence or malpractice claims.

The panel agreed that the United States should consider creating a fund for compensating individuals who are harmed in research, and consider modeling it after the Vaccine Injury Compensation Trust Fund, which provides funding for the National Vaccine Injury Compensation Program to compensate vaccine-related injury or death claims for covered vaccines. Justification for such a fund rests on the notion that research is a socially collaborative project for the social good. If someone is injured in the course of research, in which they have served the social good, they should not be left to their own devices to pay for those injuries. The presence of such a fund should not eliminate the right to litigate.

Ongoing International Dialogue

The panel agreed that its efforts over its three meetings were a critical and significant first step in sharing ideas and perspectives on how to promote ethical research conducted across borders and cultures. However, such discussions should be ongoing into the future. Thus, a forum is needed where such conversations can take place.

Closing Remarks

Dr. Gutmann thanked the panel for all of its hard work and extensive travel. She reminded the panel members that their findings and recommendations will be forwarded to the full Commission for its consideration.

A final report of the panel will consist of the proceedings from each meeting as well as the final findings and recommendations.

The Commission will convene again August 29-30, 2011, in Washington, D.C.

APPENDIX



PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES

International Research Panel

Terms of Reference

I. Introduction

In October 2010, the U.S. Government disclosed that the U.S. Public Health Service (USPHS) supported research on sexually transmitted diseases in Guatemala from 1946 to 1948 involving the intentional infection of vulnerable human populations. Concurrently, the U.S. Government announced plans to undertake two tasks: 1) conduct a thorough fact-finding investigation into the case; and 2) seek independent advice on the effectiveness of current U.S. rules and international standards for the protection of human subjects in scientific studies supported by the U.S. Government.

Subsequently, on November 24, 2010, President Obama directed the Presidential Commission for the Study of Bioethical Issues (Commission), beginning in January 2011, to “oversee a thorough fact-finding investigation into the specifics” of the USPHS supported research and to conduct a review of the adequacy of contemporary human subjects protection across the international field of research. President Obama directed the Commission Chair to convene a panel of international experts to consider current U.S. Government regulations and international standards that guard the health and well-being of participants in scientific studies supported by the U.S. Government. The President asked specifically for assurance that “the current rules for research participants protect people from harm or unethical treatment, domestically as well as internationally.”

In order to carry out this charge, the International Research Panel (Panel, or IRP) is hereby established in accordance with E.O. 13521 and 41 C.F.R. 102-3.35 as a subcommittee of the Commission to review and advise the Commission on the matters described above.

II. Purpose

The Panel will undertake a consultation process to examine the following issues:

- a. The dominant norms, and competing alternatives, driving the ethics of medical research in different global regions outside of the United States;
- b. The conflicts, if any, between U.S. norms and international standards;
- c. The challenges facing researchers conducting U.S.-funded research in global settings; and
- d. Possible strategies to address differences in regional norms for medical research.

III. Composition

- a. Qualifications
 - i. Members will be selected from the United States and the international bioethics and medical/science communities.
 - ii. A majority of members will come from outside the United States.
- b. Responsibilities
 - i. Members are expected to contribute their unique knowledge and experience in the conduct of global research, the ethical and social justice issues that exist in the current global research system, and the challenges faced by international researchers collaborating on U.S. funded research.
 - ii. Panel member contributions are based on their own experience and expertise; members are not acting as formal representatives of their countries' positions.

IV. Operations

- a. Proceedings
 - i. Decision-making shall be based on consultation and consensus.
 - ii. A final Summary of the Proceedings will be developed based on the Panel consultations.
 - iii. Meetings will be conducted in English.

b. Number of Consultations

- i. The Panel will convene for 3 in-person meetings. At least one of the meetings will take place outside the United States.
- ii. Panel Members are expected to attend at least 2 of 3 meetings.

c. Public Information

- i. A Summary of the Proceedings will be distributed publicly.

V. Term

The Consultation is expected to conclude within four months of the Panel's first meeting, however, it is understood that the Panel may meet thereafter, as needed, to complete its work before the Commission reports to President Obama.

¹ Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified in scattered sections of 21 U.S.C.) (Kefauver-Harris Amendments) (explicitly requiring informed consent in clinical investigations regulated by the U.S. Food and Drug Administration).

² Additional examples include: Joint United Nations Programme on HIV/AIDS and World Health Organization. (2007). *Ethical considerations in biomedical HIV prevention trials*, Geneva: Joint United Nations Programme on HIV/AIDS; and World Health Organization. (2010). *Guidance on ethics of tuberculosis prevention, care and control*, Geneva: World Health Organization.

³ 45 C.F.R. § 46.116(d).

⁴ *E.g.*, Joint United Nations Programme on HIV/AIDS and Global Advocacy for HIV. (2011). *Good participatory practice guidelines for biomedical HIV prevention trials 2011*. Geneva: Joint United Nations Programme on HIV/AIDS; CTSA Community Engagement Key Function Committee's Task Force. (2011). *Principles of Community Engagement: Second Edition*. Bethesda: National Institutes of Health.

⁵ *See, e.g.*, United Nations Educational, Scientific and Cultural Organization. (2005). *Universal Declaration of Bioethics and Human Rights*, Paris: United Nations Educational, Scientific and Cultural Organization: Section 12.

⁶See, e.g., Neaton, J., et al. (2010). Regulatory impediments jeopardizing the conduct of clinical trials in Europe funded by the National Institutes of Health. *Clinical Trials* 7: 705-718.

⁷ See Elger, B.S. (2008). Research Involving Prisoners: Consensus and Controversies in International and European Regulations. *Bioethics* 22: 224-238.

⁸This is consistent with the practice of many journals, which additionally require some assurance that ethical standards are adhered to during a research study, but not all publications have this requirement.

⁹ The registry was launched March 22, 2011. See EU Clinical Trials Register Goes Live. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/03/news_detail_001228.jsp&mid=WC0b01ac058004d5c1&murl=menus/news_and_events/news_and_events.jsp&jsenabled=true.

¹⁰ For example, registration in the Clinical Trials Registry of India became mandatory in June 2009. See also WHO International Clinical Trials Registry Platform. Available at: <http://www.who.int/ictrp/en/>.

¹¹ See Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115 § 113, 111 Stat. 2296 (amending 42 U.S.C. § 282).

¹² See Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85 § 801, 121 Stat. 823 (amending 42 U.S.C. § 282).

¹³ See NIH. (2000). *Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials*. Available at <http://grants.nih.gov/grants/guide/notice-files/not-od-00-038.html>.

¹⁴ See 45 C.F.R. § 46.101(h).

¹⁵ Brazilian Medical Council. (2008). *Resolution 1885/2008*. Brasilia: Brazilian Medical Council.

¹⁶ AVAC Staff. (2010). *AVAC Report 2010: Turning the Page*. New York: AVAC: Global Advocacy for HIV Prevention: 9-28.

¹⁷ Rerks-Ngarm, S., et al. (2009). Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand. *The New England Journal of Medicine* 361: 2209-2220; Dolin, R. (2009). HIV Vaccine Trial Results – An Opening for Further Research. *The New England Journal of Medicine* 361: 2279-2280.

¹⁸ Love, R.R., and N.C. Fost. (1997). Ethical and regulatory challenges in a randomized control trial of adjuvant treatment for breast cancer in Vietnam. *Journal of Investigative Medicine* 45: 423-431.

¹⁹ Joint United Nations Programme on HIV/AIDS and Global Advocacy for HIV. (2011). *Good participatory practice guidelines for biomedical HIV prevention trials 2011*. Geneva: Joint United Nations Programme on HIV/AIDS