

International Human Subjects Research Risks

**Office of Human Research Compliance Review
University of Michigan**

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Executive Summary

This report has been prepared for the university research community by the University of Michigan (UM) Office of Human Research Compliance Review (OHRCR). The focus is evaluation of human participant risks in the approval, conduct and oversight of international research studies with ongoing UM Institutional Review Board (IRB) oversight. Risks associated with human subjects research are well understood at the UM. Responsibility for managing these risks is dispersed throughout the University of Michigan (UM) Human Research Protections Program. OHRCR issues this report to summarize those risks. The recommendations are designed to assist the research community in meeting human subjects regulatory obligations as well as to advise them on evolving international ethical and regulatory expectations. Risks were informed through interviews with seven senior UM international investigators, four peer academic institutions, UM IRB leadership, UM Center for Global Health administrative leadership, the ISR/OHRCR UM “Survey of Investigator Experiences in Human Research,” and pertinent literature and websites. Data were extracted from the UM eResearch Regulatory Management System to develop a profile of UM international studies with ongoing IRB oversight. The UM Center for Global Health assisted in compilation of the UM research profile. Ethical issues in international human subjects research have traditionally focused on respect and value for cultural differences and communication norms. However, increasingly greater attention is being paid to broad challenges faced by international communities, by inequity in funding areas important to low and middle resource developing countries and to larger issues of oversight for international studies. Many developing countries have recently enacted, or are in the process of enacting, human subjects research laws and guidance. These laws are new and untested. Some developing countries are beginning to fund research subject to their new laws. Complicating the situation is the fact that human subjects protections laws and guidance may not be known or followed at regional, local and country levels. UM PIs are directly affected by these issues and are asked to interpret, and to follow, a maze-like patchwork of ethical principles, research regulations and guidance in multiple countries. Some developing countries have experienced research harms and exploitation in controversial industry funded drug development studies. Whether or not negative reactions in these countries will extend to academic research is not yet clear. Countries without human subjects guidance or regulations have challenges when researchers from several developed countries, each following their own country’s regulations, are conducting research in the country. Ethical and practical issues arise for UM researchers working with researchers from other countries and if they observe noncompliance in another country.

Summary of UM IRB Approved International Research Data

A “snapshot” of international studies with ongoing UM IRB oversight, excluding studies exempted from IRB review, was extracted from eResearch on a single day in January, 2011 (n=311). The snapshot of international research represents six percent of approximately 5,000 studies with ongoing UM IRB oversight. IRB Health Sciences/Behavioral Science (IRB-HSBS) had oversight for 69% (242) of studies, the majority of international research projects. They also approved 78% (197) of the international projects that received expedited IRB review. Far fewer studies were approved through full board review than expedited review and IRBMED had oversight for the majority of full board reviews with 71% (42) of the 59 studies that received full board review. There were very few international interventional clinical trials and the vast majority of international studies (95%) posed no more than “minimal risk” to participants. Thirty percent of the studies involved at least one vulnerable subject population as defined in US regulations. Two percent of the studies were covered by an NIH-issued Certificate of

Confidentiality (CoC). Although most studies were minimal risk studies, 41% of informed consent processes were approved with a requirement for a written, signed informed consent document. Twenty percent of all international research studies were conducted by student PIs and they accounted for nine percent of all studies with vulnerable populations. No student held a CoC. Approximately one-third of studies received federal funding. UM study sites are dispersed throughout the world. The four countries with the most UM studies are: 1) Canada [47 sites], 2) China [28 sites], 3) India [17 sites], and 4) Ghana [16 sites]. There are important differences in the IRB-HS/BS and IRBMED portfolios. IRB-HS/BS had studies in 86 different countries and 258 study sites dispersed among these countries. It also had more studies in low and middle resource developing countries. IRBMED had studies in 36 different countries dispersed among 108 sites. The schools with the most international studies resided in LS&A. The eResearch data provide valuable information that help to inform UM discussion of human subject risks in international studies. The current number of international studies is relatively low; however, with the current UM focus on international research, the volume of studies is likely to increase rapidly. UM investigators, including student investigators, are conducting studies in diverse regions throughout the world. This vast global engagement poses challenges in providing ethical and regulatory assistance for both investigators and IRBs.

International Human Subjects Risk Areas

Risk areas are categorized into seven major areas. Information discussed in these risk areas presents the issues and context for understanding the recommendations. All risk areas assume an understanding of populations, cultural norms, social contexts and governmental structures where studies take place is essential. The risk areas are:

- Risk areas in the informed consent process
- Investigator challenges and subject risks
- Risk areas in treatment studies: Standard of care and ethics of study design
- Risk areas in treatment studies: Reasonable availability of treatments
- Risks that may be mitigated by technology
- Risks in Institutional Review Board (IRBs) approval and oversight processes
- Additional areas of importance in international research

Student PI research issues are important. Discussion about UM student principal investigators (PIs) is integrated in investigator challenges and risks. In an internal 2009 UM survey, approximately 50% of UM student PIs reported their department did not have a program that helped them to understand ethical obligations conducting human subjects research.

Approximately 75% reported faculty advisors helped them to understand ethical obligations in human subjects research.

Recommendations for International Studies

A full set of recommendations with references that can assist with implementation are cited in Section VI. of this report.

A. Informed Consent Process

Highly Recommended

- i. Investigators should make more use of visual material rather than written material for informed consent processes, particularly for populations with low literacy levels or no written language.
- ii. IRBs should provide investigators examples of creative use of visual materials for informed consent processes.

- iii. IRBs should ask for back translation only for high risk studies.
- iv. Investigators should expect informed consent development to take longer, and to require more complex evaluation, than for domestic studies.

Recommended

- v. UM IRBs should consider a demonstration project of methods other than written signature to document the initial informed consent process has occurred.
- vi. As appropriate, consider linguistic status as a vulnerable subject population category.

B. Investigator Challenges

Highly Recommended

- i. Use IRB resources to access human subjects training options in commonly used international languages for international co-investigators.
- ii. In addition to the local PI, provide any international study staff and international students conducting research at the international site with training in human subject protections. Training curricula from other US institutions are readily available.
- iii. Know applicable human subjects laws and regulatory guidance in the country. Use Office of Human Research Protections (OHRP), International Compilation of Human Research Standards, World Bank and CIA World Factbook online databases for regulatory information and for overall country and societal information.
- iv. UM investigators should have local, collaborative relationships and maintain open, frequent communications regarding approval, design, conduct and dissemination of international research.

Recommended

- v. Provide international collaborators access to eResearch study information by adding them to the study and providing them with a UM friends account.
- vi. For ongoing studies monitor study implementation at international sites in order to prevent varying interpretations of the protocol and to assure protocol implementation.

C. Clinical Trials Reasonable Availability of Treatments

Highly Recommended

- i. Investigators with treatment clinical trials should develop procedures for “reasonable availability of treatments” (ancillary treatments and any ongoing treatment after a study), as appropriate.

Recommended

- ii. IRBs should consider the “fair benefits framework” to help guide ethical reviews for “reasonable availability of treatments.” (See Appendix F).

D. IRB Related Approvals and Oversight

Highly Recommended

- i. Promote use of the CITI site, which has human subjects training in several languages.
- ii. Provide investigators with more detailed guidance for responses to questions in the international section of eResearch (Section 30) in order to provide for efficient and effective IRB reviews.
- iii. When relying on international IRBs for controversial ethical issues, as appropriate, obtain information about IRB membership selection and processes used by the IRB.

- Consider whether UM IRB minutes should record how the UM IRB is using the local international site determination in its own approval process.
- iv. Continue to use health and economic indicators of organizations such as the World Bank and CIA World Factbook to help understand risks, as appropriate. Also use OHRP International Compilation of Human Research Standards.

Recommended

- v. IRBs continue to proactively suggest minor research changes that may reduce risks and make studies eligible for exempt or expedited review and for oral consent procedures.
- vi. Develop a cadre of consulting faculty in various international regions using UM international resources such as the recently developed UM Office of the Vice-Provost for International Affairs.
- vii. For resolution of controversial ethical issues, consider use of tools such as Skype to communicate with international IRBs or institutions or individuals involved in the approval process at the international site.
- viii. As global research expands, it may be useful to develop IRB configurations for IRB approvals, particularly for minimal risk studies that are specialized for oversight in various areas of the world

E. Technology

Recommended

- i. Consider feasibility of developing mobile applications for IRB submissions.
- ii. Determine feasibility and interest in using the UM eResearch platform in other countries to assist in IRB capacity building.

F. Overall

Highly Recommended

- i. Examine oversight and training for international studies with student PIs, particularly those studies with vulnerable subject populations. Consider additional vulnerabilities for linguistic and socio-economic status.
- ii. Consider restricting IRB approvals for students to co-investigator roles when there are vulnerable subject populations.
- iii. Develop a UM web portal with online resources and guidance documents for international investigators regarding human research participant protections.
- iv. Consider investment of UM resources to assist in capacity building for international investigators and IRBs where the university has ongoing, collaborative research relationships.

Recommended

- v. Survey UM investigators conducting international research to determine areas with the most need for resources and guidance in areas such as reporting abuse, illegal activity, subject payment, etc.
- vi. Tap into the international expertise of IRBs at other US universities that have relationships in regions of the world where UM may not have established IRB relationships.

I. Introduction

The Office of Human Research Compliance Review (OHRCR) has prepared this report on risks in international research for the university research community. The primary focus of the report is risks to human participants in the approval, conduct and oversight of international research. Risks described in the report are known in various parts of the university. The report provides an integrated vision of international human subjects research risks. The report is not a compilation of all current university international research related initiatives; rather, it is meant to describe important risks and, when available, provide for more specific guidance that may be useful for international researchers and university research infrastructures.

The risks (See Appendix A for types of risks) were informed through interviews with seven senior UM faculty with extensive international research experience including: the Vice-Provost for International Affairs, four peer academic institutions, Ann Arbor campus IRB leadership, UM Center for Global Health administrative leadership, literature about international research and through exploration of national and global websites. Risks were also informed by data extracted from eResearch. A “snapshot” of current IRB approved international studies in the eResearch data warehouse on January 11, 2011 was used to develop a profile of international studies by UM faculty. Staff from the Center for Global Health assisted in compiling the UM eResearch international research profile.

The report does not explore in depth all ethical issues in the approval or implementation of specific research topics in the international research context, for example, international stem cell research or biospecimens are not discussed. Rather, it provides an overview of risk areas the UM community can use to examine current knowledge and practices.

The literature about ethical issues in planning and conducting international research and in IRB oversight is extensive and growing rapidly. References cited in the report are examples of literature that explores international issues.

II. Background

Research has already gone global; largely before any international human subjects ethical guidelines or regulations have been widely accepted or implemented. Thus, investigators and university research infrastructures alike are left with a maze-like patchwork of regulations and guidance from the United States (US) and other countries. Just as driving laws such as speed limits may not be followed in many countries, investigators may, or may not, be knowledgeable about existence, interpretation and application of regulations for human subjects protections at country, regional and local levels (Pritchard, 2010).

Multiple human subjects regulatory issues present challenges. For any US federally funded international study, US human participant research protections regulations must be followed. International sites engaged in the research funding must obtain federal assurances of ethical study conduct. Unfortunately, some specific US federal human participant regulations may not be easily adaptable to local cultural contexts. In low and middle-resource developing countries, for example, the requirement for a written and signed informed consent form may not be easily culturally translatable. Some middle resource developing countries such as India and Brazil, have recently developed their own human subjects research regulations, which means US funded

research conducted in these countries must conform to both US regulations and to new, untested regulations in these countries. China has adopted an extensive set of guidances for health research. The guidances are not legally binding regulations as they are in the United States.

UM faculty reported additional evolving international issues that can affect day-to-day work of US researchers. For example, UM investigators may be present at an international site and working side-by-side with researchers from another developed country. The researchers from the other developed country may conduct activities that would not be approved by a US IRB, and, the activities they undertake may reflect on all researchers in the region. Drugs, devices and biologics industries are also rapidly going global. A typical late stage investigational drug trial is now being conducted in 70 or more developing countries (Getz & Zuckerman, 2010). However, once the drugs, devices or biologics are approved in a developed country, they may not be readily accessible, or even available, in the countries where clinical trials were conducted. Academic researchers are concerned about perceptions of investigator initiated studies in regions where industry studies may be the “norm.”

There are world-wide guidance documents on ethical conduct of clinical trials supported by entities such as the World Health Organization (Council for International Organizations of Medical Sciences, 2002), or the World Medical Association (World Medical Association, 2009; World Medical Association Inc, 1964) There are no world-wide regulatory guidance documents for socio-behavioral researchers. In fact, some developed countries such as the Netherlands have no regulations at all for socio-behavioral studies. Guidance for risks in international socio-behavioral studies can be found in disciplinary literature and at some US federal agencies. Socio-behavioral research risks can be particularly complex to sort out because of diversity in topics studied, the wide range of disciplines involved, the variety of methods used and the frequent inclusion of vulnerable participants.

Given the complex issues and differing societal norms and cultural contexts, disagreement and miscommunication in international research is highly probable. Ethical principles, although culturally dependent, provide critical touch points for discussing and resolving troublesome ethical issues in international research (Macklin, 2008). Common ground is developing around a consensus that substantive principles such as ethical principles in the US Belmont Report (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979), provide standards and should be universally applied (European Medicines Agency, 2011; Fadare & Porter, 2010). With differing opinions and conflict, it may also be helpful to distinguish between ethical principles and procedural requirements. For example, ethical principles in the Belmont Report give rise to the requirement to obtain informed consent. Procedural requirements specify how consent is obtained, for example with a written signature. Distinguishing between ethical and procedural requirements provides respect for cultural variation and helps to clarify differing positions regarding research practices and helps to provide resolution for disagreements (Macklin, 2008; National Bioethics Advisory Commission, 2001).

III. University of Michigan IRB Approved eResearch International Data

A. Methods for UM Data Extractions of Studies with Ongoing IRB Oversight

A “snapshot” portfolio of all currently approved UM international studies with ongoing IRB oversight was extracted from the eResearch warehouse on a single day, January 11, 2011. Studies exempted from ongoing IRB oversight were not included. Studies in the eResearch data

warehouse were coded as international studies if an international country was listed as a performance site (eResearch Question 3-1.3) and if any questions in the international section of eResearch, Section 30, were completed by the PI. For each study, the following data were extracted:

- Type of IRB review, e.g. expedited or full board
- UM IRB with oversight
- PI category as faculty/other and student
- PI plans for international travel
- Risk level of the study, e.g., minimal risk, minor increase over minimal risk (MIOMR), moderate risk and high risk
- Type of funding, e.g., federal, internal/no funding and non-federal funding
- Type of informed consent, e.g., written and oral/waiver of informed consent
- Whether or not vulnerable subjects as defined in the US regulations (prisoners, pregnant women, neonates and children) were in the study population, and
- Whether or not a certificate of confidentiality was issued for the study

There was difficulty identifying international studies for data extraction. The “country” field for international performance sites (eResearch Question 3-1.3) was not a required eResearch field and some studies may have been missed. This issue was reported to UM MAIS. “Country” has subsequently been added as a required field for each performance site.

One additional strategy was used to identify international studies. If an investigator answered any questions in Section 30, the eResearch international section, data for that study were also extracted. This resulted in the addition of some studies for which investigators answered international questions although their study had no international performance sites. These studies were deleted from the sample.

The sample did not include international studies classified as exempt from IRB oversight in the US human subjects regulations. There is no eResearch field to identify international studies exempt from human subjects regulations. Only currently approved studies with ongoing IRB oversight were included in the final sample. No expired studies were included.

B. Analysis of UM International Data with Ongoing Oversight

International sites by IRB.

There were a total of 311 IRB approved international studies, excluding exempt studies, in the eResearch warehouse. At any given time, there are approximately 5,000 approved studies at UM. The total international studies represent approximately 6% of UM IRB approved studies. The majority of these international studies, 214 studies or 69% have UM IRB-HSBS oversight. This represents about 16% of the HSBS total research portfolio which numbers approximately 1300 studies. IRBMED approved 91, or 29%, of all studies representing about 2% of their total research portfolio of approximately 3600 studies. The Flint and Dearborn IRBs together have oversight for approximately 100 studies. Dearborn approved five international studies and Flint IRB approved one (See Appendix B. Figure 1).

Expedited and full board review processes.

The IRB approves a study using expedited or full board review processes. A majority of the studies, 81% (252), received expedited IRB review and the rest were full board reviews. IRB-

HSBS approved a majority, 78% (197), of the total of expedited studies and approximately 30% (17) of full board studies. IRBMED approved a greater proportion of full board studies, 71% (42) and 20% (49) of expedited studies (See Appendix B. Figure 2).

Faculty and student PIs.

Faculty or other UM staff made up 80% (249) of the PIs in the sample (See Appendix B. Figure 3). Students made up 20% (62) of the sample and 92% (57) of students had IRB-HSBS oversight. Sixty percent (133) of faculty and 97% (59) of students planned to travel internationally (See Appendix B. Figure 4).

Risk levels.

The risk level for international studies is low with 94% (289) of studies approved as minimal risk studies and 6% (17) approved as greater than minimal risk. Two studies, less than 1% of total studies were approved as high risk studies and both were approved by IRBMED (See Appendix B. Figure 5). All student studies were approved as minimal risk studies.

Funding source.

Human subjects regulatory requirements follow all federally funded studies. Approximately 100 or 32% of all studies had some federal funding. Students with federal funding make up approximately 4% (11) of the total of 311 studies and they are 18% (11) of all student PIs (See Appendix B. Figure 6). Studies may have more than one funding source.

Informed consent process: Oral/waiver vs. written.

There were 617 informed consent processes approved for the 311 international studies. Studies may have more than one population and more than one informed consent process per study. An IRB can waive some, or all, of the elements of informed consent and the written documentation of informed consent or it can require written consent and written documentation of consent. UM IRBs approved oral consent or waivers for 56% (344) of the informed consent processes and it approved written informed consent for 41% (255). The rest of the types of informed consent processes stored in eResearch could not be categorized. The various informed consent options were not clear. Classification of informed consent processes resulted in a few categories being listed in an “other” category (See Appendix B. Figure 7).

Vulnerable subject inclusion.

Inclusion of vulnerable subjects in a study population is one indicator of a possible increase in sensitivity to undue influences during the research process. For this report, vulnerable subjects were categorized as one of the populations addressed in the US regulations, and included prisoners, pregnant women, fetuses, neonates and children. Approximately 30% (101) of the studies had at least one population of vulnerable subjects. Faculty/other PIs were conducting 91% (92) of studies with vulnerable subjects while students were conducting 9% (9) (See Appendix B. Figure 8).

Certificate of confidentiality.

Another measure of participant risk is whether or not a study has a certificate of confidentiality. Certificates of Confidentiality are issued by the US National Institutes of Health (NIH) and they protect identifiable research information from forced disclosure. Only six studies, approximately 2% of studies, had a US certificate of confidentiality indicating research data contained

confidential information that posed risks for subjects if exposed. Faculty held all of the certificates of confidentiality. While a certificate of confidentiality assists in protection of confidential data in the US, it is not likely to have any substance internationally.

University areas with the most international studies.

As expected, the health and behavioral science IRB had the most international studies and LSA had the most departments with international studies. The Anthropology Department had the most international studies with 46 studies. The Psychology Department had 16 studies and Epidemiology and Sociology each had 13 studies (See Appendix C. Table I). The distribution of student PIs among departments with international studies was very similar to the distribution of PIs overall (See Appendix C. Table II).

Information about international sites.

Most studies, 88% (275), were taking place at one international site and 12% (36) were taking place at multiple sites (See Appendix C. Table III). The number of international sites ranged from one to eight (See Appendix C. Table IV). The twelve countries where the most overall UM studies are being conducted are listed in Table V in Appendix C. These twelve countries represent less than one-half of all international sites. UM study sites are dispersed throughout the world. The four countries with the most UM studies are; 1) Canada [47], 2) China [28], 3) India [17], and 4) Ghana (16). However, there are important differences between IRB HS/BS and IRBMED. IRB HS/BS has studies in 86 different countries with 258 study sites dispersed among the countries (See Appendix C. Table VI). It also has more studies in low and middle resource developing countries. IRBMED has studies in 36 different countries dispersed among 108 sites. (See Appendix C. Tables VII and VIII).

C. Discussion Points

- International research represents a relatively low proportion of the total number of studies with UM IRB oversight.
- IRB-HSBS receives the large majority of international studies and the most exempt studies. IRBMED approved the most full board studies although there are not large numbers of studies that receive full board review.
- While some countries have several UM study sites, most studies represent a wide range of disciplines and are dispersed throughout the world. For human subjects protections, this leads to IRB burden locating appropriate consultants and challenges for investigators in obtaining assistance about human subjects regulations and guidance in other countries.
- The majority of international studies are low risk and are approved as minimal risk studies.
- Although nearly 95% of studies are approved as low risk studies, written informed consent is required for 41% of studies. This may represent an issue identified earlier in this report regarding a preference in US regulations for written informed consent documentation.
- Students represent 20% of PIs doing international studies. While all of their studies are minimal risk, some do have vulnerable subject populations and a few have certificates of confidentiality. The student PI group, particularly those with a

vulnerable population and certificate of confidentiality may be at greater risk in understanding and applying human subjects protections due to complexities and risks of research in international settings.

- The percent of studies with vulnerable subjects or US certificates of data confidentiality are indicators that a substantial minority of international studies represent risk to subjects in the areas of informed consent and data protections. The assumption is that US certificates of confidentiality are not useful outside of the US.
- Approximately 2/3 of international studies have no federal funding which would allow for UM demonstration projects for international studies, particularly in the area of informed consent.
- The eResearch warehouse categorization of informed consent is not clear and categorization of informed consent processes is complex.

IV. Risk Areas

The following sections are organized around risk areas. The source of information for the risk is organized in sub points under the major risk heading. The overall major risks are:

- Risk areas in the informed consent process
- Investigator challenges and subject risks
- Risk areas in treatment studies: Standard of care and ethics of study design
- Risk areas in treatment Studies: Reasonable availability of treatments
- Risks that may be mitigated by technology
- Risks in Institutional Review Board (IRBs) approval and oversight processes
- Additional areas of importance in international research

A. Risk Areas in the Informed Consent Process

- i. The informed consent process must be sensitive to local cultural context, making the process and informed consent documents more time consuming to develop (Committee on International Collaborations in Social and Behavioral Sciences Research, U.S. National Committee for the International Union of Psychological Science, Board on International Scientific Organizations, Policy and Global Affairs, & National Research Council of the National Academies, 2008) and to test, in particular, when there is no written language for the population.

UM Investigator Feedback

A UM investigator is conducting international informed consent research with language using a neutral human figure on a computer touch screen. The animated computer figure goes through motions that describe the informed consent process (Haig et al., 2009).

Literature

Newsprint page diagrams without text have been used to describe informed consent for illiterate participants in Guatemala (Research Triangle Institute International, 2005).

“Spheres of consent” may extend to: tribal leaders, village elders, extended family, and heads of households, which results in a layered consent process with multiple levels of input and permissions (E. J. Emanuel, Wendler, Killen, & Grady, 2004; Frimpong-Mansoh, 2008).

UM Investigator Feedback & Literature.

Length of time permissions for the research and participant informed consent usually takes longer than in the US.

IRB leadership.

The IRB often struggles, and has difficulty, finding experts to give input on IRB ethical decisions.

- ii. US regulations require a written signature unless the requirement for written signature is waived. In many countries, written signatures have different meanings than in the US. They can imply binding contractual obligations when there is none, can cause illiterate subjects to decline study participation, can be a catalyst developing mistrust where there is fear of reprisals, and lastly, can be an insult. A signature requirement can unknowingly put subjects at risk or can invalidate research if there is poor study participation because of a signature requirement. While much low risk research may qualify for a waiver of signature with US regulations, many do not.

UM Investigator Feedback, Literature & Peer Institutions.

Investigators report very strong negative feedback about the difficulties this requirement presents for many international studies.

- iii. Back translation may not be useful to participant understanding, may be cumbersome, may be expensive and should not be a standard requirement.

UM Investigator Feedback.

Back translation is sometimes helpful, but more often is not useful. It is often difficult to find two people who speak the same dialect; one to prepare consent and one to back translate. Back translation may not detect issues in participant understanding and can be time consuming and expensive.

Peer Institutions.

Rather than back translation, “translation attestation form” may be used by investigators with lower risk studies. This form was developed at the Harvard School of Public Health. The PI attests that IRB approved study documents are accurately translated into a language understandable to study participants.

Literature.

There is great difficulty in getting appropriate back translations. Back translations are often not practical, for example, over 200 language dialects are spoken in Nigeria alone (Fadare & Porteri, 2010).

- iv. Participants may choose to participate in studies and do not understand differences between research and voluntary participation with an understanding of research risks and risks of standard clinical care.

Literature

This is reported as an issue for all clinical trials, and, may be compounded in international settings where there is little exposure to research among the general population (Srinivasan, 2009).

- v. Research participation may not be voluntary when national and local socio-political environments are hierarchical, when populations have not had experience with electoral type of representation and when populations have experienced problems such as conflict

with their government. Research participation also may not be voluntary if local culture and context are not understood, for example, when respected authority figures promote research participation.

UM IRB Leadership and Literature

There can be difficulty in understanding the national and local context and culture to do an ethical and regulatory review of research. For example, in clinical trials, health care providers may be compensated by a federal government or susceptible to corruption and have undue influence in enrolling study participants (Harris, 2010). Payment amounts for research activities may be an undue inducement or coercive in middle and low resource countries. Compensation should be for expenses related to participation and not for the degree of study risk. Amount of compensation can provide undue inducement to enroll in studies, particularly health related studies. Examples of undue inducement or coercion come from China where indigent rural villagers were paid for genetic samples and did not understand the research (Sleeboom, 2005). Undue inducement can occur when a country has few health care services for indigent populations. For example, in India health care is paid out-of-pocket. There are approximately 1,000 clinical trials registered with the Indian government and there have been reports of violations of participant's research rights (Overdorf, 2011; Shetty, 2011).

B. Investigator Challenges and Subject Risks

- i. Strong international collaborative partnerships provide for culturally appropriate research designs, subject population protections and integrity in research conduct.

UM Investigator Feedback & Literature

Both report the importance of having a collaborator or co-investigator in the international country.

- ii. UM investigators have concerns about whether they have access to the culturally appropriate knowledge and tools to resolve ethical issues in the everyday management and oversight of international human subjects research.

UM Investigator Feedback

Some UM investigators reported uncertainty in managing ethical issues that arise, and where to get assistance for issues such as local undue influence to participate in research, abuse reporting, etc.

- iii. International collaborators often lack sufficient access to education in their own language about research ethical principles, regulations and guidance in both their own country and the US.

UM Investigator Feedback

PEERRS was not perceived as available in common international languages; PIs had concerns about the knowledge level and research practices of international co-investigators regarding human subjects protections.

- iv. US investigators and international collaborators often lack knowledge about oversight and enforcement of research regulations and of ways to monitor studies to proactively provide feedback to international sites.

Literature

International collaborators and study staff often are not in possession of knowledge about research regulatory environment at international sites ("Duke Medicine and Kaplan EduNeering Partner to Build Global Expertise in Clinical Trials," 2011).

UM Investigator Feedback

One UM investigator interviewee department does not allow students to conduct research in an international country without an international collaborator or mentor at the international site. The ISR/OHRCR 2009 survey (Pennell & Lepkowski, 2010) of principal investigators revealed approximately one half of students agreed their department had an effective mentoring program that taught students about ethical obligations and three quarters said their faculty advisor helped them to understand the ethics of conducting research with human participants.

UM IRB Leadership

Leadership expressed concerns about student knowledge and ability to make appropriate participant protections decisions onsite at the international site and student safety onsite.

Peer Research Institutions.

Student investigators may not provide appropriate human subject participant protections if faculty mentoring, monitoring and oversight is not sufficient. A peer research institution does not allow students as PIs of any studies with IRB oversight. The faculty person must be the PI (See Johns Hopkins Bloomberg School of Public Health IRB, Policy 103.24, Principal Investigators http://www.jhsph.edu/bin/q/b/JHSPH%20IRB%20Policies_updated_08Sept10.pdf)

C. Risk Areas in Treatment Studies: Standard of Care and Ethics of Study Design

Risk areas for this section and for Section D, Reasonable availability of treatments, represent areas of evolving international standards. As a whole, they are indicative of the increasing role of health care research in global justice (Ijsselmuiden, Kass, Sewankambo, & Lavery, 2010).

- i. Study participants may be at risk from differing standards of care in developed and developing countries. The concept of "standard of care", itself is ill defined. It can be considered the most commonly used treatment, the best available treatment or a treatment that should be provided. It can also be considered the treatment advocated by experts in the field or the treatment reimbursed by third party payers (Hyder & Dawson, 2005; Soren & Harris, 2008). For example, the National Bioethics Advisory Commission used the term, "treatment that is routinely available" instead of "standard of care" in their 2001 report on International clinical research and considered whether or not that care was affordable, accessible or acceptable (National Bioethics Advisory Commission, 2001). Standard of care issues are often unclear and present intense ethical issues in international studies. Participants in developing countries may find they are choosing; 1) between care provided through research and limited, or no, comparable clinical care or, 2) placebo controlled studies that might be ethical in a developing country and would not be considered ethical in a developed country or, 3) new procedures that are commonly used in a developed country and not available or known outside of research in a developing country.

UM Investigator Feedback and Literature

One UM investigator reported high levels of concern, and outright suspicion, in some developing countries about "double standards" in research, particularly clinical trials,

financed or sponsored by developed countries and conducted in developing countries. This is a major area of ethical concern in international clinical trial literature (Hawkins, 2008).

OHRCR Review of UM International Research Data

Overview of UM eResearch data reveals a very small minority of the studies are randomized controlled trials. However, this area of research is likely to expand at UM.

Guidance Documents

Guidance documents may or may not be helpful. For example, the World Medical Association “The Declaration of Helsinki” (World Medical Association Inc, 1964), states participants in a control group should receive the best proven diagnostic and therapeutic methods. In some cases, this means providing control groups with care they would have in developed countries rather than the standard care they would receive in their own developing country. This can be a useful standard or very problematic. It could even lead to poorer care. For example, standards of care in developed countries may dictate use of research diagnostic equipment or treatment devices that require a stable electrical supply. Reliance on this equipment would be problematic in some countries and would drive the standard of care.

D. Risk Areas in Treatment Studies: Reasonable Availability of Treatments

- i. Reasonable availability of treatment for participants in clinical studies is a major issue in international research. Generally, this refers two areas: 1) reasonable availability of treatment that maintains overall health and treats illnesses and is not directly related to the research while a study is being conducted and, 2) availability of the treatment when the study ends. Those treatments not directly related to the research are also known as “ancillary” care. For example, a participant in an oncology study for bladder cancer must have available treatments for any bladder infection that might arise. Ongoing availability of treatments, drugs or devices when a study ends may not be available for study participants if the developing country has poorly resourced public health institutions.

Literature

The topic of reasonable availability of treatments in international clinical trials is highly controversial with many ethicists in developed countries promoting availability and some low and middle resource countries demanding availability both during, and at the end of, research participation (Participants in the Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries, 2008).

Ancillary clinical care can be essential to maintain the health of study participants. Whether this care is available depends on the nature of study, the population and the capacity of the local health system. Ancillary treatment agreements should be considered and planned before a study begins (Participants in the Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries, 2008).

Funding for reasonable availability of treatments is complicated by the fact that US federal research funding will not generally cover ancillary care and treatments after a study ends.

Health problems that affect developed countries are studied in developing countries where public health systems have fewer resources for ancillary care and ongoing care. The World Medicine Association describes a 10/90 gap in medical research. Only ten percent of global research funding is spent on health problems that affect 90% of the world's population (World Medical Association, 2009).

The International Ethical Guidelines for Biomedical Research Involving Human Subjects, developed by the Council for International Organizations of Medical Sciences (CIOMS) and whose development was supported by the World Health Organization lists reasonable availability of treatment at the end of a trial as a criterion for the ethical conduct of international clinical trial (Council for International Organizations of Medical Sciences, 2002).

Arguments for reasonable availability may not be realistic in all cases. A “Fair Benefits” (E.J Emanuel, 2008) ethical decision-making framework has been proposed. The framework is based on determining the social value of the research, fair subject selection with participants in poverty or not overly represented in the sample (unless the research is related to those topics), and research risks are justified by the benefits or research risks are acceptably low.

E. Risks that May be Mitigated by Technology

This section addresses risks that may be mitigated by technology. The risks associated with breaches of data confidentiality are addressed elsewhere at the university.

- i. There are risks in the conduct of research if accurate and substantive information about local context, culture, country regulations and guidance are not available.

Peer Institutions

Some IRBs at peer institutions are using Skype to discuss particularly difficult ethical issues with local international IRBs or with constituents at international sites.

- ii. There may be risks to subjects when accurate and timely submission of adverse events and protocol amendment changes are difficult such as when investigators are in the field in low resource developing countries.

Literature

Developing countries are experiencing growth in use of mobile programs with wireless technology. Mobile IRB submission programs are not yet available through Click Commerce.

- iii. IRB capacity building through technology

In countries where there are established, collaborative research relationships with the UM and where sites hold a US Federal Wide Assurance (FWA) and receive US federal funding, it may be possible for IRBs in these countries to develop a platform for access and use of the UM eResearch Click Commerce program for their own IRB submissions and approvals. Individual international investigators currently have access to UM eResearch when they are listed as members of the study team.

F. Risks in IRB Related Approvals and Oversight

- i. The UM IRB may not have accurate knowledge of regulations, local context and culture to make the best IRB determination (Pritchard, 2010).

UM Investigator Feedback

This area is of concern to UM investigators. The importance of IRB review is appreciated. A perception is that the IRB is overly concerned about some ethical areas and not concerned enough about other ethical areas. In addition, investigators rely on the IRB to help untangle rules and provide standard criterion that assure the study will be conducted in a manner that meets US regulations, their own institutional policies and procedures and the regulations and standards of the international research site.

Literature

A survey of US investigators doing international biomedical clinical research has reported perceptions that IRBs focus on procedural concerns and appear less focused on ethical concerns (Kass, Dawson, & Loyo-Berrios, 2003; Kass & Hyder, 2001).

IRB Leadership

Knowledge of regulations in other countries, local societal norms and cultural contexts and in particular, freedom of participants for voluntary participation is the most difficult area for IRBs in the review of international studies. IRB leadership works to find experts other than the PIs to provide consultations regarding local cultures. However, independent consultations can be difficult to obtain. For example, knowledge of minority cultures in a country may be limited to only a few investigators in the US or in the world. IRBs must frequently communicate with investigators to ask them to provide them more information about the international study, local culture and regulations, relationships at the site, benefits and risks, etc. This reduces IRB efficiency and can extend IRB review times.

OHRCR Review of eResearch International Questions.

OHRCR analysis of selected responses to the eResearch International Questions in section 30 revealed investigators frequently provide short responses that may not provide enough information for the IRB to make their regulatory decisions. A question remains about whether or not the IRB receives information that provides for effective and efficient IRB decision making.

Obama Commission on the Study of Bioethical Issues.

Testimony at a 2011 session of President Obama's *Commission on the Study of Bioethical Issues* noted investigators conducting international studies are frustrated trying to figure out which rules they need to follow. At times this results in lack of follow up on promising research or a need to shift the burden to other entities to ensure the research is compliant (Zakaib, 2011).

- ii. UM IRBs may rely on IRBs in other countries for some or part of the information for IRB review. The quality of their review is not often known.

Literature.

IRBs in many countries are poorly resourced and do not have in depth experience or knowledge of IRB functions. They also may not have independent reporting structures (Coleman & Bouesseau, 2006; Rehnquist, 2001).

The quality of IRB review is dependent upon ethics committee membership, the standards and interpretation of standards applied in the review, whether or not protections for vulnerable populations are understood and whether or not any ongoing, continuing review is being done.

In July of 2011 an IRB in India was chastised by the Indian Government for approving a study inconsistent with India's IRB research regulations. There were irregularities in recruitment processes for poor, illiterate participants (Overdorf, 2011; Shetty, 2011).

Resources to assist in development, to administer and to accredit IRBs in developing countries are available (Council for International Organizations of Medical Sciences, 2002; Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP), 2010; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996; Karlberg & Speers, 2010).

There are growing numbers of international sites with US Federal Wide Assurances (FWA) issued by the Office of Human Research Protections (OHRP) in the US Health and Human Services. In 2008, the last year of available data, 2,405 or 23% of all active FWAs were for international sites. However, an FWA is not a guarantee of the quality of IRB review. In 2008 OHRP conducted evaluations on 0.2% of international institutions with an FWA (Pritchard, 2010).

iii. Other IRB Areas/Information

IRB approval must be done according to US IRB regulations which are different than investigator regulations. They describe criteria the IRB must follow to approve a study. For example, they must assure study risks have been minimized and document it in the IRB minutes. If an investigator does not provide the IRB with culturally-specific knowledge they have in their possession and that the IRB might not have, a study could go to full board review rather than expedited review. Conversely, a study might be expedited by the IRB when it should be sent to full board.

IRB-HSBS reports proactive work with students and faculty to exempt studies and to provide opportunity for oral consent in order to prevent negative experiences for subjects and to reduce unnecessary burden for investigators.

There is no variable to track exempt international studies in eResearch.

IRBs across the US are building established relationships with various countries and their IRBs. This information is not widely known or shared. For example, the University of Washington IRB has relationships with IRBs in Vietnam while Columbia University has arrangements with a consortium of IRBs in South Africa.

G. Additional Areas of Importance in International Research

i. Equivalent protections.

US federal regulations have a clause allowing reliance on foreign IRBs if they have protections equivalent to US federal human subjects regulations. This clause has never been used (Pritchard, 2010). Large numbers of UM studies are done in Canada where there is strong regulatory oversight. As the federal government examines regulatory burden, a likely country where the US could recognize equivalent protections would be Canada, a country with significant numbers of UM studies.

ii. Long term use of research findings.

In US federal regulations IRBs do not to make study approval decisions based on possible future uses of research findings.

Literature

It is possible international research study findings could be used in ways that cause discomfort or distress, may not accurately portray participants or may jeopardize participants or populations in the future.

V. Summary

In summary, research risks in international research are substantial, complex, and continue to evolve. Attention to research risks and to their mitigation is imperative to assure international participants, populations and communities are not harmed or exploited. Following current US regulations provides a standard, but may add to risks, for example in the area of informed consent where cultures vary from the US. International research risks extend beyond the boundaries of the university's research oversight infrastructure. Mitigation must rely on thoughtful, informed judgments or investigators may drop promising lines of research or may not be able to rise to ethical challenges in protecting human research participants.

VI. Recommendations

A. Informed Consent Process

Highly Recommended

- i. UM investigators should develop innovative and creative informed consent processes that are culturally relevant to the study population (Research Triangle Institute International, 2005). Consider use of visual materials instead of written materials. Consider oral consent processes whenever possible.
- ii. IRBs should provide investigators with examples of innovative use of visual materials to replace written materials for the informed consent process ranging from low-tech serial newsprint pictorials (Research Triangle Institute International, 2005) to animated computer touch screens (Loar, Haig, Yamakawa, & Baljinnnyam, 2011).
- iii. IRBs and investigators consider implementation of the Translation Attestation Form (See Appendix G) being used by a peer institution. Use back translation only for high risk studies.
- iv. Investigators should expect developing the informed consent process takes more time to prepare and will likely need more feedback and evaluation for international studies, in particular those with populations with low literacy levels or no written language.

Recommended

- v. UM should consider a demonstration project for non federally funded studies of alternative methods to document informed consent rather than written documentation. Thoughtful references on a possible process for this demonstration exist (Wendler, 2001).
- vi. Consider linguistic status as a vulnerable subject population category, as appropriate.

B. Investigator Challenges

Highly Recommended

- i. Explore with the IRB, as appropriate, online human subjects training options in different languages for international investigators. See Collaborative IRB Training Initiative (CITI) investigator training for modules in international language (Collaborative IRB Training Initiative (CITI)).
- ii. When international study staff or international students assist with studies at an international site, consider additional human subjects training. See curriculum for investigators and community participants at Family Health International, 2nd Edition, The first edition is available in five languages (Rivera & Borasky, 2009). See research ethics training curriculum at the Johns Hopkins School of Public Health. The Human Subjects Research Ethics Field Training Guide (Johns Hopkins University IRB Office, 2009; Merritt et al., 2010).
- iii. Explore local international site laws and their implementation, regulatory guidance, and local cultural context before submitting an application to the UM IRB. In particular provide information about risks and benefits, as well as the informed consent process, which helps the UM IRB to make an efficient and appropriate review. Assist in communication and coordination with international IRBs. As appropriate, use university international resources and information such as Office of Human Research Protections (OHRP) International Compilation of Human Research Standards (Office for Human Research Protections (OHRP), 2012), World Bank

Country Health and Economic Indicators (The World Bank, 2011), CIA-The World Factbook (Central Intelligence Agency, 2011) and the World Health Organization Country Information (World Health Organization, 2011) as aids in developing study procedures as appropriate.

- iv. UM investigators should have local, collaborative relationships and maintain open, frequent communications regarding approval, design, conduct and dissemination of international research (Robinson, Baron, Heise, Moffett, & Harlan, 2011).

Recommended

- v. Provide international collaborators access to eResearch study information by adding them to the study team and providing them with a UM friends account.
- vi. For ongoing studies monitor study implementation at international sites in order to prevent varying protocol interpretations and to assure protocol implementation.

**C. Clinical Trials Reasonable Availability of Treatments and Ancillary Treatment
Highly Recommended**

- i. Investigators with treatment clinical trials develop procedures for “reasonable availability of treatments”, during and at the end of clinical trials before a trial begins, as appropriate (Participants in the Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries, 2008).

Recommended

- ii. IRBs consider the “fair benefits framework” (E.J Emanuel, 2008) to help guide ethical review of ancillary treatments and treatments at the end of a study when approving international clinical treatment studies (See Appendix F).

D. IRB Related Approvals and Oversight

Highly Recommended

- i. Promote the use of CITI online modules in common international languages as an alternative to UM PEERRS at <http://www6.miami.edu/citireg/>. Some UM faculty are not aware of online human subjects training in common world languages.
- ii. Provide investigators with more detailed guidance in Section 30, the international section, embedded in eResearch to enhance information about what to submit to facilitate an accurate, efficient IRB review (Fitzgerald, Wasunna, & Pape, 2003). Consider increasing guidance in the areas of collaborative relationships, risks, types of benefits, if any, and include population or community benefits and information that assures informed consent is voluntary (See appendix D for current eResearch questions; See Appendix E for information to help guide development of eResearch international research guidance).
- iii. When relying on local international IRBs for controversial or difficult ethical issues, if at all possible, ask specific questions about IRB membership, the standards applied in review, continuing review, and any additional vulnerable population’s protections, if applicable. Clearly state in UM IRB minutes how the UM IRB is using the local international site determination in its own approval process.

- iv. Continue to use health and economic indicators of organizations such as the World Bank Health and Economic Indicators and The CIA World Factbook in study reviews as appropriate.

Recommended

- v. Develop a cadre of consulting faculty with authentic international relationships in areas of the world most commonly used by UM investigators. Use resources such as the UM Center for Global Health and the UM Office of the Vice Provost for International Affairs for assistance.
- vi. IRBs should continue to proactively suggest oral consent procedures to investigators who are not using it, as appropriate to US human subjects regulations. IRBs should also continue to work proactively with faculty and students on ways to minimize risks of study procedures and informed consent processes to provide for exemptions from human subjects regulations as appropriate.
- vii. When relying on local IRBs or constituencies to approve a study with difficult or controversial ethical issues, consider use of communication technologies, such as Skype to obtain more information from the local site, as appropriate.
- viii. As global research expands, it may be useful to develop IRB configurations for IRB approvals, particularly for minimal risk studies that are specialized for oversight in various areas of the world.

E. Technology

Recommended

- i. Consider developing mobile applications for IRB submissions.
- ii. Determine feasibility and UM interest in using the UM eResearch platform to assist other countries in building IRB capacity. Consider access to eResearch for IRBs in resource challenged areas of the world.

F. Overall

Highly Recommended

- i. Catalyze university discussion about risks in international studies when students are principal investigators. Consider examination of oversight and training of students. For example, one UM department does not approve student research in countries if there is not an international mentor or US mentor who assures resources and support at the international site.
- ii. Consider restricting IRB approvals for students to co-investigator roles rather than PI roles when the study has vulnerable populations.
- iii. Develop a UM web portal with online resources and guidance documents for international investigators for human research participant protections. See Johns Hopkins Bloomberg SPH: Resources for IRBs/RECs Involved in International Research (Johns Hopkins Bloomberg School of Public Health, 2011), NIH: Fogarty International Center Bioethics Information and Resources (Fogarty International Center, 2011) and National Science Foundation (NSF): Office of International Science and Engineering, International Research Integrity (Office of International Science & Engineering, 2011).

- iv. Consider resources or grants, education and communications that assist in capacity building for investigators and for IRBs where the university has established, international collaborative relationships (Kennedy et al., 2006; Sleem et al., 2010).

Recommended

- v. Survey investigators who conduct international research to determine areas where resources and guidance are most needed. Consider topics such as knowledge of country laws and culture, abuse reporting, international IRB submissions or ethics review, informed consent translation and documentation, mentoring and oversight of students conducting international research.
- vi. Catalyze a national discussion about ways US universities might network with other universities with established relationships with international IRBs. Tap into the international expertise of IRBs at other US universities that have relationships in regions of the world where UM may not have established IRB relationships.

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VIII. Appendices

Appendix A – Benefits and Harms in Social/Behavioral Science

Table A: Summary of Harms and Ameliorative Measures*

Kind of Harm	Minimal	Minor Increase over Minimal	Major	Ways to Ameliorate
Inconvenience	Boring, interruption	Unexpected major involvement		Adequate informed consent
	Most vulnerable are those with complicated lives or time constraints.			
Physical Harm	Transitory or very minor injury	First aid may be indicated	Violent assault, life threatening**	Appropriate safety considerations
	Most vulnerable: Those in contexts in which there are safety issues.			
Psychological Harm				
Worry (warranted or otherwise)	All of these psychological harms are highly idiosyncratic in occurrence and degree of harm, and difficult to predict. Sensitive administered informed consent can give persons an opportunity to decline if feeling particularly fragile and vulnerable. Post-research procedures (debriefing and desensitizing, offering counseling, making referrals) can ameliorate or prevent harms and turn unpleasant experiences into lasting benefits. These are excellent opportunities for subjects to learn and grow from the experience; debriefing should be educational and nurture personal insight and wisdom. Reiteration of confidentiality measures taken to prevent disclosure may be useful after participation in some research. Deception and concealment, especially with powerful induction to involve self in upsetting or reprehensible acts is ameliorated by initial consent to concealment with promise of total debriefing. An alternative, when studying aggressive or other reprehensible behavior is to study response to heavily induced desirable behavior (e.g., disobedience to authority).			
Upset, depression				
Embarrassment				
Shame or Guilt				
Loss of Self-Confidence				
Disrespectful Treatment of Subjects	This is an attribute of the researcher or the research treatment that may cause any of the other above forms of psychological harm. Effective respectful congruent communication (not a consent form) is essential.			
Most vulnerable: those who are immature or emotionally fragile.				
Social Harm	Transitory embarrassment	Short-term minor stigma, conflict	Long-term stigma or scapegoating	Confidentiality & privacy protected
	Most vulnerable: those with something to hide.			
Economic Harm	Loss of a few \$\$s	Short-term loss of financial opportunity	Loss of credit, insurance, job, loss of lawsuit	Compensate minor harm, assure privacy & confidentiality
	Most vulnerable: those in need of relevant forms of financial security			
Legal Harm	Involvement with law enforcement	Misdemeanor conviction	Subpoena of damaging data, felony conviction	Certificate of Confidentiality, anonymity
	Most vulnerable: those involved in studies of illegal behavior and those currently involved in legal action relating to the research (whose data might be subpoenaed by the prosecution or opposing party).			

*Table prepared for the Social and Behavioral Sciences Working Group on Human Research Protections by Joan E. Sieber, Working Group member (January 2004).

**Major harms of this nature are secondary.

Appendix B – University of Michigan IRB related International Research Data

Figure 1. - Percent of International Studies by UM IRB

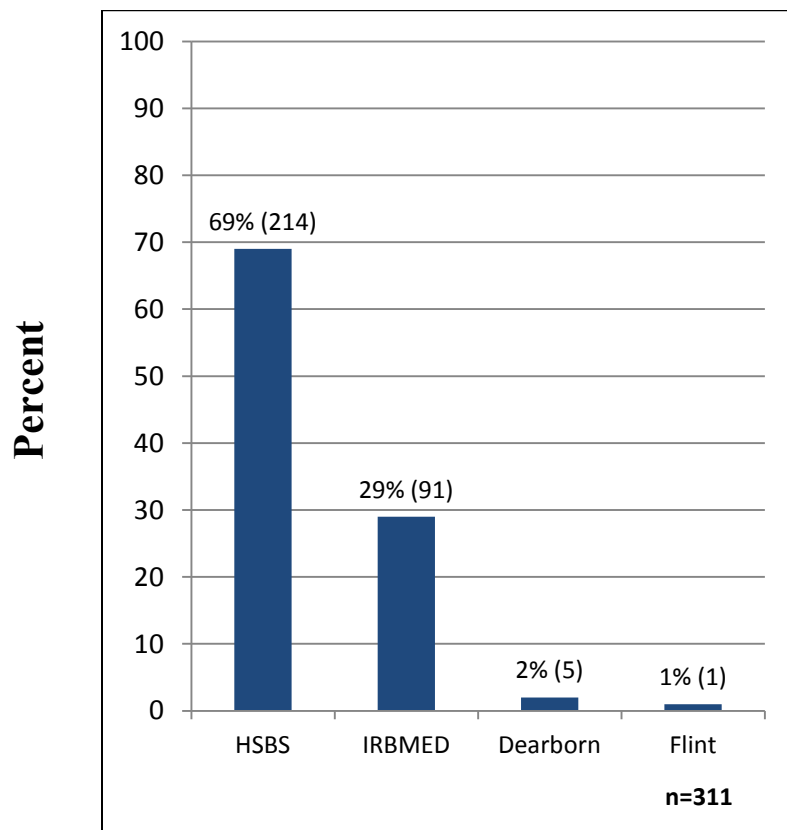


Figure 2. – Expedited and Full Board Reviews by UM IRB

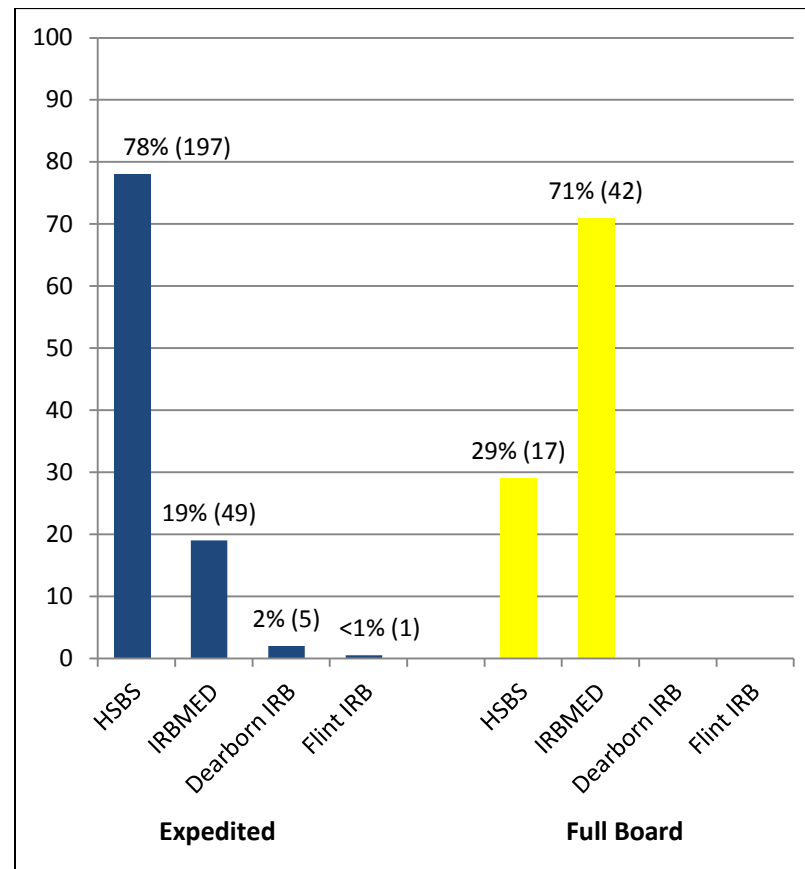


Figure 3. - International Studies by Faculty/Other PIs & Student PIs

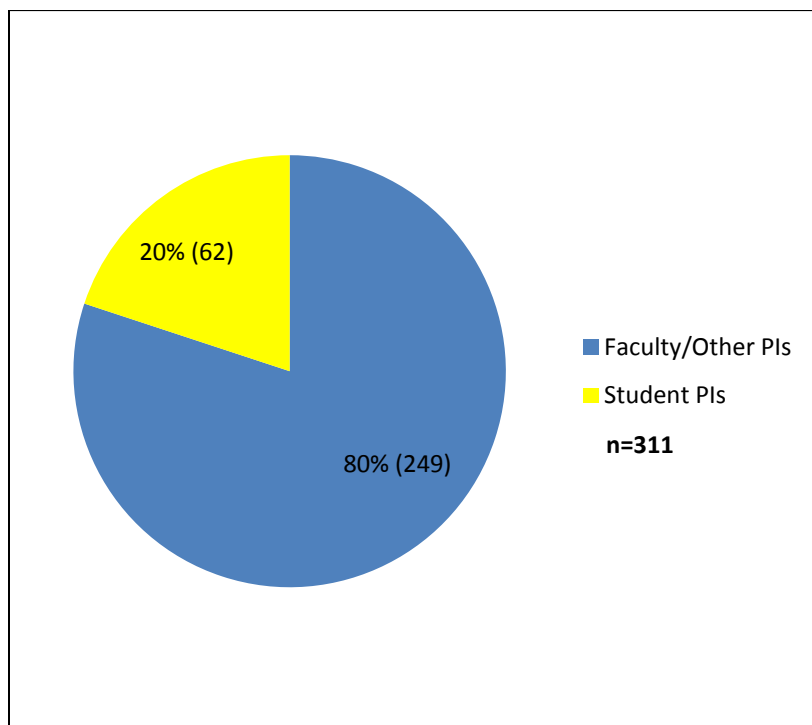


Figure 4. - Plans for Travel to International Site by Investigators

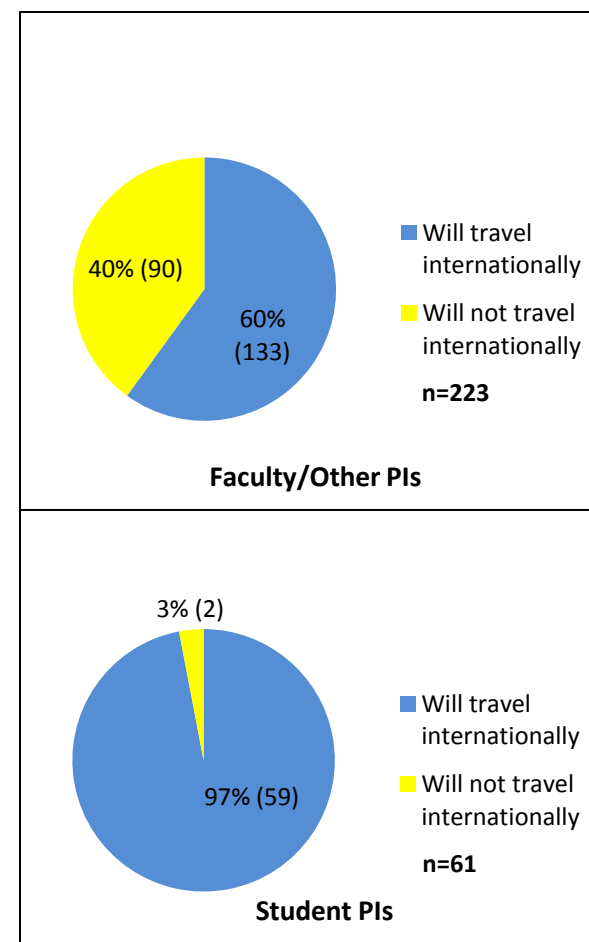


Figure 5. - Risk Levels of International Studies

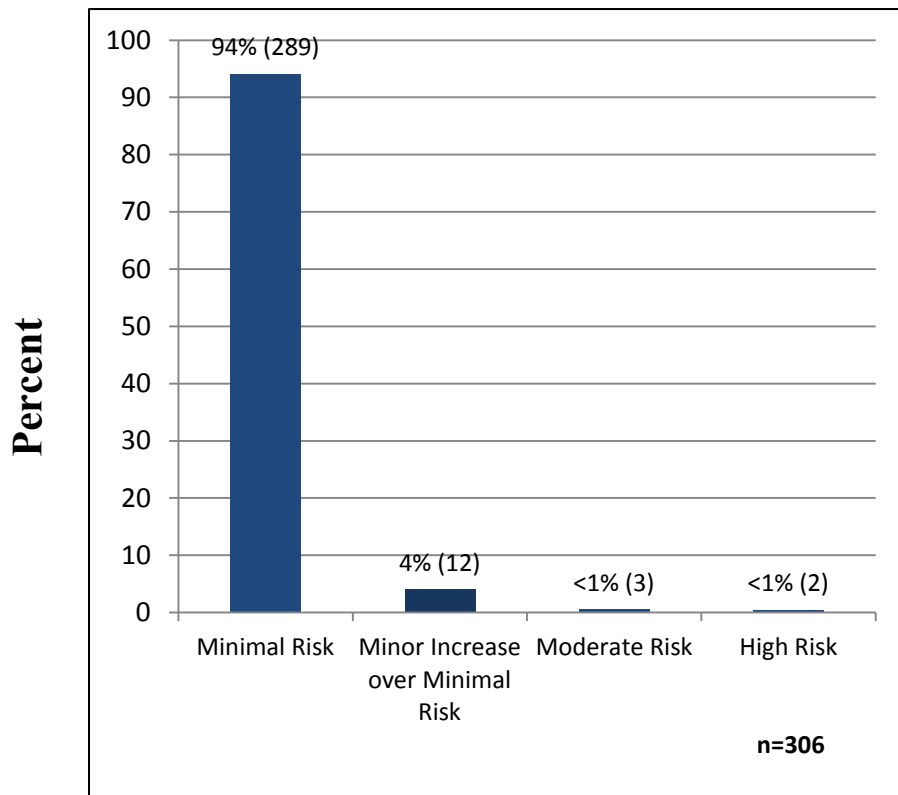


Figure 6. - Studies with and without Federal Funding

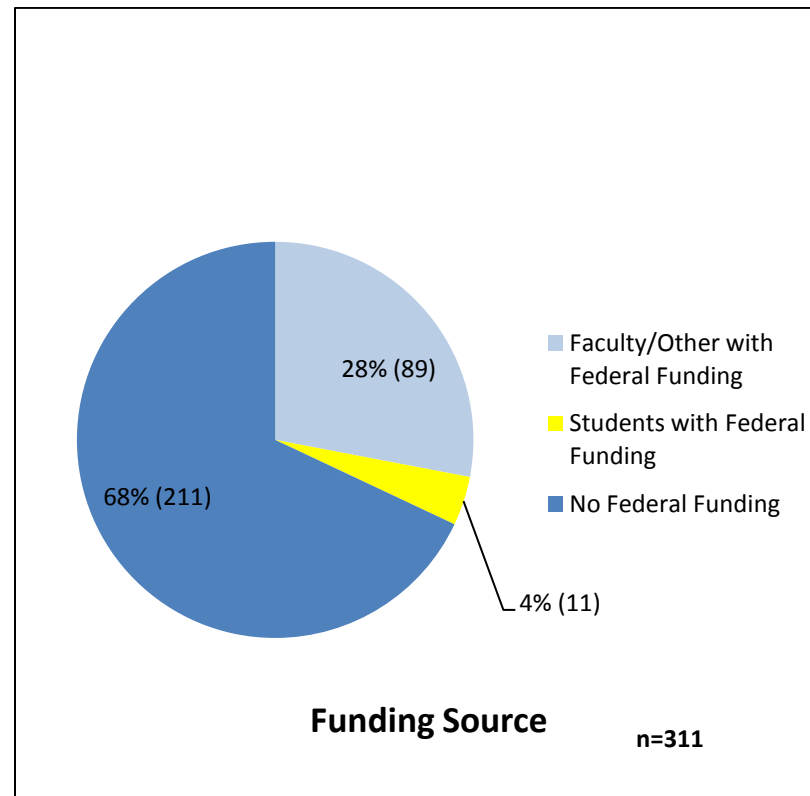


Figure 7. - Written vs. Oral/Waived Informed Consent Process

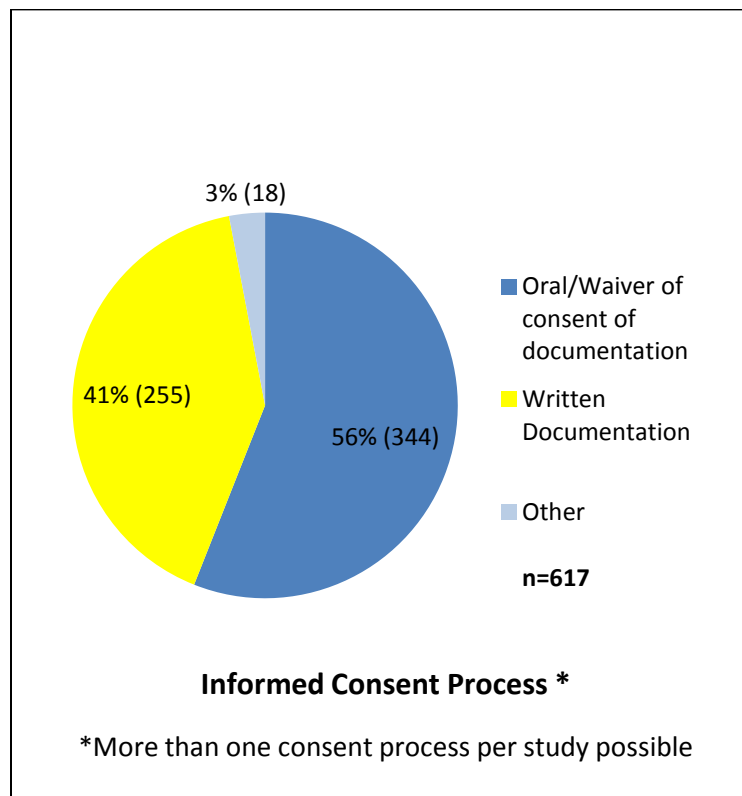
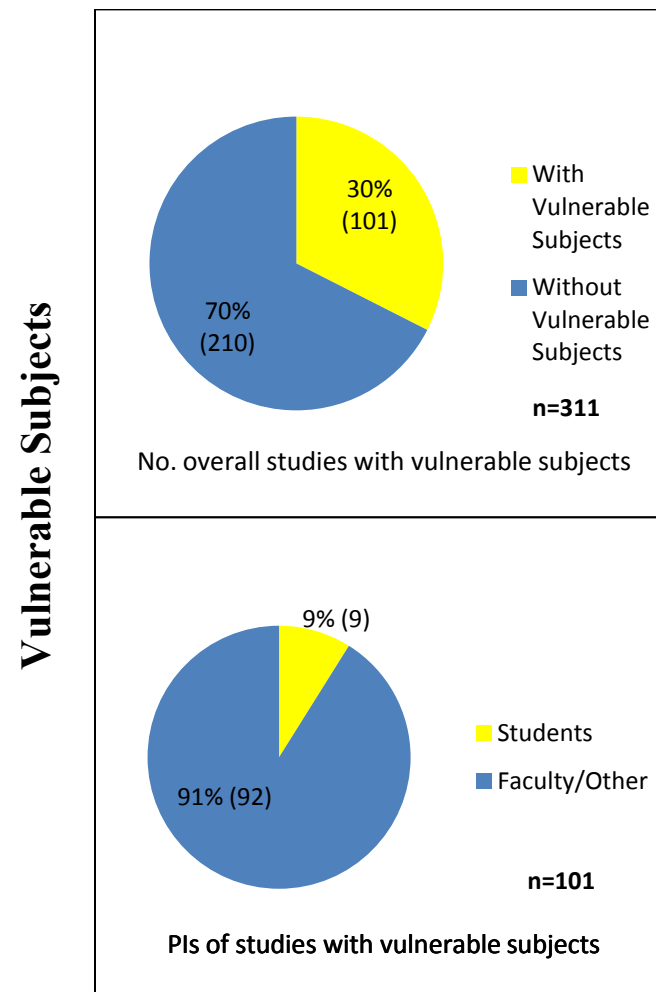


Figure 8. - Inclusion of US Regulatory Defined Vulnerable Populations by Investigator*



*US Regulatory Vulnerable Subjects - prisoners, pregnant women, fetuses, neonates and children

Appendix C – University of Michigan International Research Site Data

Table I. Rank order of Ten UM Departments with the most international studies with IRB oversight

Ten UM Departments with most Int'l Studies		
No.	Department	Count
1	Anthropology Department	46
2	LS&A Psychology Department	16
3	Epidemiology Department	13
4	LS&A Sociology Department	13
5	G. Ford Sch of Public Policy	12
6	Internal Medicine Department	12
7	Ctr for Human Growth & Dev	10
8	Environmental Health Sciences	10
9	Population Studies Center	10
10	Sch of Nat Resources & Env	8

Table II. Rank order of Ten UM Departments with the most student PIs with international studies and IRB oversight

Ten Departments with most Student PI Int'l Studies		
No.	Department	Count
1	Anthropology Department	14
2	LS&A Political Science Dept	6
3	Epidemiology Department	3
4	LS&A Sociology Department	3
5	SNRE Office of Academic Progs	3
6	Internal Medicine Department	2
7	LS&A Dept of Linguistics	2
8	LS&A Economics Department	2
9	LS&A Psychology Department	2
10	Population Studies Center	2

Table III. Count of the number of international performance sites per study

Count of Int'l Sites per Study	
One site	Multiple Sites
275	36

Table IV. Descriptive data on number of international performance sites for studies

Description of Number of Int'l Sites per Study					
Count of studies	Min	Max	Mean	SD	Median
311	1	8	1.2	0.72	1

Table V. Twelve countries with the most UM studies

Countries with the most UM studies		
No.	Department	No. of Studies
1	Canada	47
2	China	28
3	India	17
4	Ghana	16
5	Japan	15
6	Germany	11
7	United Kingdom	10
8	Mexico	10
9	Israel	10
10	Uganda	9
11	Nepal	7
12	Malawi	7

Table VI. Number of countries and number of sites by UM IRB

UM IRB	No. of Unique Countries with Int'l UM Sites	Total No. Int'l Sites	Percent Total Int'l Sites
IRBMED	36	108	29%
IRB HS/BS	86	258	69%
IRB Dearborn	6	6	2%
IRB Flint	1	1	0%
Total	129	373	100%

UM Health Sciences and Behavioral Sciences IRB	Country	Count
UM HS/BS	China	22
UM HS/BS	India	16
UM HS/BS	Japan	12
UM HS/BS	Canada	11
UM HS/BS	Germany	9
UM HS/BS	Nepal	7
UM HS/BS	Malawi	7
UM HS/BS	Uganda	7
UM HS/BS	Israel	7
UM HS/BS	Ghana	7
UM HS/BS	Kenya	6
UM HS/BS	Mexico	6
UM HS/BS	Tanzania	6
UM HS/BS	Egypt	5
UM HS/BS	Philippines	5
UM HS/BS	Colombia	5
UM HS/BS	Australia	4
UM HS/BS	Peru	4
UM HS/BS	Guatemala	4
UM HS/BS	Brazil	4
UM HS/BS	Bolivia	4
UM HS/BS	Ecuador	3
UM HS/BS	Mali	3
UM HS/BS	Morocco	3
UM HS/BS	Korea (Republic of)	3

UM Health Sciences and Behavioral Sciences IRB, cont'd	Country	Count
UM HS/BS	United Kingdom	3
UM HS/BS	Singapore	3
UM HS/BS	South Africa	3
UM HS/BS	Taiwan, Republic of China	3
UM HS/BS	Spain	3
UM HS/BS	Indonesia	3
UM HS/BS	Italy	3
UM HS/BS	Dominican Republic	2
UM HS/BS	Cuba	2
UM HS/BS	Cape Verde Islands	2
UM HS/BS	Hong Kong	2
UM HS/BS	Switzerland	2
UM HS/BS	Tunisia	2
UM HS/BS	Haiti	2
UM HS/BS	Bulgaria	2
UM HS/BS	Russia	2
UM HS/BS	France	2
UM HS/BS	Papua New Guinea	2
UM HS/BS	Venezuela	2
UM HS/BS	Nigeria	2
UM HS/BS	Belgium	1
UM HS/BS	Bangladesh	1
UM HS/BS	Mozambique	1
UM HS/BS	El Salvador	1
UM HS/BS	Lebanon	1
UM HS/BS	Ethiopia	1
UM HS/BS	Namibia	1
UM HS/BS	Liberia	1
UM HS/BS	Europe	1
UM HS/BS	Kyrgyz Republic	1
UM HS/BS	Nepal	1
UM HS/BS	Luxembourg	1
UM HS/BS	Argentina	1

UM Health Sciences and Behavioral Sciences IRB, cont'd	Country	Count
UM HS/BS	Jordan	1
UM HS/BS	Western Samoa	1
UM HS/BS	Vietnam	1
UM HS/BS	United Arab Emirates	1
UM HS/BS	Ukraine	1
UM HS/BS	Chile	1
UM HS/BS	Iraq	1
UM HS/BS	USA, Canada	1
UM HS/BS	Turkey	1
UM HS/BS	Thailand	1
UM HS/BS	Afghanistan	1
UM HS/BS	Honduras	1
UM HS/BS	Suriname	1
UM HS/BS	Algeria	1
UM HS/BS	Cambodia	1
UM HS/BS	Senegal Republic	1
UM HS/BS	Senegal	1
UM HS/BS	Ireland	1
UM HS/BS	Saint Lucia	1
UM HS/BS	Greece	1
UM HS/BS	Rwanda	1
UM HS/BS	Reunion Island	1
UM HS/BS	Poland	1
UM HS/BS	Pakistan	1
UM HS/BS	Finland	1
UM HS/BS	Norway	1
UM HS/BS	Fiji Islands	1
UM HS/BS	Netherlands	1
Total HSBS UM Study Sites/Country		258

*More than one site possible per study

Table VIII. Count of UM study sites by country for UM IRBMED (more than one site per study possible)*

IRBMED	Country	Count
IRBMED	Canada	35
IRBMED	Ghana	9
IRBMED	United King	7
IRBMED	China	5
IRBMED	Poland	4
IRBMED	Mexico	4
IRBMED	Israel	3
IRBMED	Ecuador	3
IRBMED	Chile	3
IRBMED	Sweden	2
IRBMED	Spain	2
IRBMED	Peru	2
IRBMED	Japan	2
IRBMED	Honduras	2
IRBMED	Germany	2
IRBMED	France	2
IRBMED	Uganda	2
IRBMED	Zambia	1
IRBMED	Venezuela	1
IRBMED	Syria	1
IRBMED	Sri Lanka	1
IRBMED	South Africa	1
IRBMED	Qatar	1
IRBMED	Papua New G	1
IRBMED	Pakistan	1
IRBMED	Nicaragua	1
IRBMED	India	1
IRBMED	Egypt	1
IRBMED	Costa Rica	1
IRBMED	Colombia	1
IRBMED	Taiwan	1
IRBMED	Brazil	1
IRBMED	Botswana	1
IRBMED	Belgium	1
IRBMED	Australia	1
IRBMED	Turkey	1
Total IRBMED UM Study Sites		108

Table IX. Count of UM study sites by country for UM Dearborn IRB

UM Dearborn IRB	Country	Count
Dearborn	Lebanon	1
Dearborn	Taiwan, Republic of China	1
Dearborn	Canada	1
Dearborn	China	1
Dearborn	Spain	1
Dearborn	Australia	1

Table X. Count of UM study sites by country for UM Flint IRB

UM Flint IRB	Country	Count
Flint	Japan	1

Appendix D – eResearch Questions

The screenshot shows a Firefox browser window displaying a web form. The address bar shows the URL `https://eres-sandbox.dsc.umich.edu`. The page header includes the text "eResearch REGULATORY MANAGEMENT SAND" and "App HUM00". Below the header, there is a navigation bar with "Most Visited", "Getting Started", "Latest Headlines", and "Bookmarks". The main content area is titled "30. International" and contains the following questions and options:

30. International

Completion of this section is required based on the response provided to question 3-1.1.

30.1* Will the principal investigator be traveling to another country to conduct the research?
 Yes No Clear

30.1.1* Will the PI be able to communicate with the IRB from the site?
 Yes No Clear

30.2* Which research procedures will be performed at the foreign site(s)?
 All research procedures
 Only a subset of research procedures. Describe below.

30.3* Describe any special arrangements to protect subject confidentiality at the foreign site(s).

30.4* Describe the study team's knowledge of the local culture and community.

30.5* Describe any additional local or customary permissions required in order to contact subjects and/or conduct this research?

Appendix E – What Makes Research in Developing Countries Ethical: The Benchmarks of Ethical Research

What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research

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(See the editorial commentary by Kuritzkes, on pages 794–5.)

In recent years, there has been substantial debate about the ethics of research in developing countries [1–5]. In general, the controversies have centered on 3 issues: first, the standard of care that should be used in research in developing countries [6–13]; second, the “reasonable availability” of interventions that are proven to be useful during the course of research trials [14–19]; and third, the quality of informed consent. The persistence of controversies on such issues reflects, in part, the fact that existing ethical guidelines can be interpreted in multiple ways, are sometimes contradictory, or rely on unstated, yet controversial, ethical principles [6, 7, 9–11, 13, 20–24].

To provide unified and consistent ethical guidance, we apply a previously proposed ethical framework for clinical research within developed countries to developing countries, explicating a previously implicit requirement for collaboration [25]. More importantly, we propose specific and practical benchmarks to guide researchers and

research-ethics committees in assessing how well the enumerated ethical principles have been fulfilled in particular cases.

MINIMIZING EXPLOITATION

An ethical framework for multinational research should minimize the possibilities of exploitation [25]. A exploits B when B receives an unfair level of benefits or unfair burden of risks as a result of interacting with A [25, 26]. In developed countries, the risk of exploitation of subjects or host communities is minimized, because society funds research to improve health, researchers and research institutions are part of the larger community, and there is an infrastructure, even if imperfect, that translates research results into health-care practices for the benefit of the larger community. Research in developing countries creates a greater risk of exploitation: individuals or communities in developing countries assume the risks of research, but most of the benefits may accrue to people in developed countries [27]. Although poverty, limited health-care services, illiteracy, cultural and linguistic differences, and limited understanding of the nature of scientific research neither cause nor are necessary for exploitation, they increase the possibility of such exploitation [16–20, 26–28]. Furthermore, the regulatory infrastructures and independent oversight processes that might minimize the risk of exploitation

may be less well established, less supported financially, and less effective in developing countries. Guidelines for ethical research should minimize the risk of exploitation under these circumstances [28].

BEYOND PRINCIPLES TO BENCHMARKS

Previously, we delineated a framework for ethical research that included 7 principles [25]. However, an ethical framework for research in developing countries must provide more than broad principles. As Macklin notes, underlying the apparent “harmony [on principles] we confront unanswered questions, as well as stark disagreements” [29, page 19]. Accordingly, we add an eighth principle—collaborative partnership—and elaborate these principles through 31 benchmarks that systematically specify practical measures to determine the extent to which the research satisfies the principles (table 1) [30, 31].

This framework of principles and benchmarks is complex, because ethical evaluation of clinical research is complex. A single ethical principle is rarely absolute; most situations implicate multiple principles [32–34]. Consequently, the various principles and benchmarks will compete and must be balanced against each other—a process that inevitably requires judgment [30, 32–34].

Importantly, this framework functions

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The views expressed are those of the authors, reflecting their own personal research, and do not necessarily reflect the views or policies of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services of the US Government.

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Table 1. Ethical principles and benchmarks for multinational clinical research.

Principles	Benchmarks
Collaborative partnership	<p>Develop partnerships with researchers, makers of health policies, and the community.</p> <p>Involve partners in sharing responsibilities for determining the importance of health problem, assessing the value of research, planning, conducting, and overseeing research, and integrating research into the health-care system.</p> <p>Respect the community's values, culture, traditions, and social practices.</p> <p>Develop the capacity for researchers, makers of health policies, and the community to become full and equal partners in the research enterprise.</p> <p>Ensure that recruited participants and communities receive benefits from the conduct and results of research.</p> <p>Share fairly financial and other rewards of the research.</p>
Social value	<p>Specify the beneficiaries of the research—who.</p> <p>Assess the importance of the health problems being investigated and the prospective value of the research for each of the beneficiaries—what.</p> <p>Enhance the value of the research for each of the beneficiaries through dissemination of knowledge, product development, long-term research collaboration, and/or health system improvements.</p> <p>Prevent supplanting the extant health system infrastructure and services.</p>
Scientific validity	<p>Ensure that the scientific design of the research realizes social value for the primary beneficiaries of the research.</p> <p>Ensure that the scientific design realizes the scientific objectives while guaranteeing research participants the health-care interventions to which they are entitled.</p> <p>Ensure that the research study is feasible within the social, political, and cultural context or with sustainable improvements in the local health-care and physical infrastructure.</p>
Fair selection of study population	<p>Select the study population to ensure scientific validity of the research.</p> <p>Select the study population to minimize the risks of the research and enhance other principles, especially collaborative partnership and social value.</p> <p>Identify and protect vulnerable populations.</p>
Favorable risk-benefit ratio	<p>Assess the potential risks and benefits of the research to the study population in the context of its health risks.</p> <p>Assess the risk-benefit ratio by comparing the net risks of the research project with the potential benefits derived from collaborative partnership, social value, and respect for study populations.</p>
Independent review	<p>Ensure public accountability through reviews mandated by laws and regulations.</p> <p>Ensure public accountability through transparency and reviews by other international and nongovernmental bodies, as appropriate.</p> <p>Ensure independence and competence of the reviews.</p>
Informed consent	<p>Involve the community in establishing recruitment procedures and incentives.</p> <p>Disclose information in culturally and linguistically appropriate formats.</p> <p>Implement supplementary community and familial consent procedures where culturally appropriate.</p> <p>Obtain consent in culturally and linguistically appropriate formats.</p> <p>Ensure the freedom to refuse or withdraw.</p>
Respect for recruited participants and study communities	<p>Develop and implement procedures to protect the confidentiality of recruited and enrolled participants.</p> <p>Ensure that participants know they can withdraw without penalty.</p> <p>Provide enrolled participants with information that arises in the course of the research study.</p> <p>Monitor and develop interventions for medical conditions, including research-related injuries, for enrolled participants at least as good as existing local norms.</p> <p>Inform participants and the study community of the results of the research.</p>

within general ethical values, such as honesty, that are relevant to scientific integrity and avoidance of fraud [30, 31]. In addition, these principles and benchmarks must be specified before there can be any enforcement mechanism. We cannot determine how to enforce until we determine what to enforce.

COLLABORATIVE PARTNERSHIP

A collaborative partnership between researchers and sponsors in developed countries and researchers, policy makers, and communities in developing countries helps to minimize the possibility of exploitation by ensuring that a developing country determines for itself whether the research is acceptable and responsive to the community's health problems [28]. Moreover, without the engagement of researchers and host communities in the developing country, a study is unlikely to have any lasting impact, and, without the investment of makers of health policies, the research results are unlikely to influence policy making and the allocation of scarce health-care resources. A collaborative partnership also demonstrates awareness of and respect for cultural differences [35].

What constitutes a collaborative partnership? Six benchmarks seem to be essential (table 1). First, it requires partners—representation of parties in the developing country. Second, it requires collaboration—sharing responsibility for assessing the importance of the health problem and the value of the research to the community, for planning and conducting the study, disseminating the results, and ensuring that they are used for health improvements.

Third, a collaborative partnership requires mutual respect. This entails recognition of and respect for the host community's distinctive values, culture, and social practices, which should be incorporated into the design and implementation of the study. Importantly, respect does not

mean uncritical acceptance of practices that might be oppressive or coercive.

Fourth, a true collaborative partnership aspires to minimize disparities between researchers and sponsors from developed countries and the host community, at least disparities related to the research project. This could occur through development of health-care research resources and investment in the health-care sector, such as assistance with training of researchers and health-care workers, development and implementation of standard operating procedures for both clinical research and ethics review, and the establishment of a system for independent ethical review of research proposals.

Fifth, the community in which the research is being conducted should receive fair benefits from the conduct and/or results of the research [28]. Such benefits might include employment and training for community members to augment health-care services for the entire community [28]. Sixth, collaborative partnership requires a fair distribution of the tangible and intangible rewards of research among the partners. Very little can generate more resentment, mistrust, and a sense of exploitation than unfair distribution of the benefits of collaboration. This may require agreements on sharing intellectual property rights, royalties, and other sources of financial profit, as well as appropriate authorship and other credit for contributions to the research.

SOCIAL VALUE

It is widely recognized that ethical clinical research must have social value, through generation of knowledge that can lead to improvements in health; without social value, research exposes participants to risks for no good reason and wastes resources [25, 36]. However, the process of translating research results into health improvements is complex, incremental, and haphazard [37]. Typically, early studies are valuable only because the infor-

mation they generate informs additional research that cumulatively could change health care. Priorities may change while a study is being conducted, and the cooperation of diverse groups is often needed to make changes on the basis of research results. Consequently, determinations of social value are always uncertain and probabilistic, entailing judgments about the usefulness of a sequence of research [37]. Even in wealthy countries with well-established research and health-care infrastructures, research results are imperfectly incorporated into clinical practice. These problems are more complex in developing countries, where health-care infrastructures and funding are less well supported and developed. Consequently, the social value of research for the host community must be explicitly specified and enhanced.

Four benchmarks ensure social value. First, it should be determined who will benefit from the research. It is important to delineate the prospective beneficiaries of the research study, specifying whether they include the local community from which research participants will be enrolled, the host country, or people outside the host country.

Second, the potential value of the research for each of the prospective beneficiaries should be outlined. Each potential beneficiary may rank the health problem's importance differently. For example, because malaria is a substantially greater health problem for certain developing countries than for developed countries, improvements in interventions for cerebral malaria may be of substantial value to people in developing countries, whereas research on prophylactic medications for malaria will be more valuable for tourists from developed countries, and a malaria vaccine may be of substantial value to everyone.

Third, it is important to develop mechanisms to enhance the social value of research. Through collaborative partnerships, strategies should be devised to disseminate results in appropriate languages

and formats to key stakeholders, including the local community, health policy makers, health-care providers, and international health-care organizations. This may require not only presentations at scientific conferences and publications in journals but also novel forms of dissemination, such as presentations at community gatherings [35]. Social value can also be enhanced when research is integrated into a long-term collaborative strategy, so that the research project forms part of a more comprehensive research and health-care delivery strategy to address significant health problems.

Fourth, the conduct of the research should not undermine the community's existing health-care services. Beyond this minimal requirement, supplementing the existing system through the provision of additional resources, equipment, medications, or training appropriate to the research can enhance value.

SCIENTIFIC VALIDITY

Science and ethics do not conflict; valid science is an ethical requirement [25, 37]. Unless research generates reliable and valid data that can be interpreted and used by the specified beneficiaries of the research, it will have no social value, and participants will be exposed to risks for no benefits [25, 37]. In addition to the standard requirements for valid research, such as adequate sample size and unbiased measurement of outcome, multinational research should fulfill 3 benchmarks.

First, a research study must be designed so that the results will be useful in the context of the health problem in the developing country [29]. Interventions should be selected to ensure that the design is useful in identifying effective or appropriate interventions; implementing socially, culturally, and economically appropriate changes in the health-care system; or providing a reliable foundation for conducting subsequent research. Interventions are selected to ensure that the design will realize social

value and that the data are generalizable to the host community [38].

Second, the study design must realize the research objectives while neither denying health-care services that participants are otherwise entitled to nor requiring services that are not feasible to deliver in the context of the country's health-care system [10–12, 37, 39]. Determining entitlement to medical services in studies is challenging, because entitlements differ among countries [40, 41]. Even in wealthy countries, participants are not entitled to every available or effective medical service, because justice necessitates establishing priorities [41, 42]. For instance, it is widely accepted that cardiac research should not be required to include a coronary care unit, because participants would not be entitled to this service under a just distribution of resources [9, 10, 12, 43]. Conversely, in a study evaluating interventions to reduce mortality from cerebral malaria conducted in rural settings where travel to hospitals is impracticable, provision of bed nets may be part of a valid design, even if participants may not otherwise have them [44]. If the study's objective is deemed to be socially valuable, especially to the enrolled participants' community, demands for providing more-comprehensive interventions beyond those to which participants are entitled or beyond those that are feasible and sustainable may be unethical if they undermine the scientific objectives or make the results irrelevant to the community.

Third, the study must be designed to be feasible, given the social, political, and cultural environment in which it is being conducted [12]. Ensuring feasibility might require sustainable improvements to the health-care infrastructure, such as training of personnel, construction of additional facilities, or provision of an affordable drug.

FAIR SUBJECT SELECTION

Historically, populations that were poor, uneducated, or powerless to defend their

own interests were targeted for high-risk research, whereas promising research was preferentially offered to more-privileged individuals [25]. A challenge for research in developing countries is fair selection of target villages, tribes, or city neighborhoods from which individual participants will be recruited. First, at a minimum, the study population should be selected to ensure valid science [25]. Scientific reasons for choosing a particular community might be high prevalence, incidence, or transmission rates of an infection, special drug-resistance patterns, or particular combinations of diseases.

Scientific considerations alone will usually under-determine which community or individuals are selected. Second, minimizing risk is essential. For instance, in selecting a target population for an HIV vaccine study, a community that does not discriminate against HIV-infected persons and that can provide treatment for opportunistic infections is preferable. Third, the community should be one in which a collaborative partnership can be developed and in which social value can be realized. Consequently, it is preferable to select communities that have established or that are capable of establishing a system for identifying legitimate representatives and that will share responsibility for planning and conducting the study and ensuring that results are implemented through health system improvements or additional research.

Fourth, factors such as familial coercion, social marginalization, political powerlessness, and economic deprivation must be considered, to determine the vulnerability of communities or groups within the community [45]. For instance, if health policy makers suggest a particular tribe, the researchers should determine that the group has been selected for good reasons, such as a high incidence of disease, not because of social subjugation. If a scientifically appropriate population is identified as vulnerable, specific safeguards to protect the population should be imple-

mented, such as ensuring confidentiality and the freedom of potential research participants to decline joining the study.

FAVORABLE RISK-BENEFIT RATIO

All clinical research should offer participants a favorable risk-benefit ratio, or, if potential risks outweigh benefits to participants, the social value must justify these risks [25, 46]. Only benefits that accrue to participants from the interventions necessary to achieve the research objectives or those deriving from the knowledge to be gained by the research should be used to justify risks to participants [25, 47].

Two benchmarks unique to developing countries apply. First, the risk-benefit ratio for individuals must be favorable in the context in which they live. The underlying risks of a particular disease can vary because of differences in incidence, drug resistance, genetic susceptibility, or social or environmental factors. When participants confront a higher risk of disease, greater potential benefits may justify greater risks in research design [48]. Similarly, the risk-benefit ratio for a particular study may be favorable in communities where the social value of the research is high but may be unfavorable where potential value is lower [25, 51].

Second, the risk-benefit ratio for the community should also be favorable. To make this assessment, the risks and potential benefits for the community, such as increased antibiotic resistance or collection of sensitive information, must be specified. Benefits might include the information obtained from the study, services provided to participants, or improvements in the health of the community. Furthermore, to be consistent with collaborative partnership, the community should determine whether the risks are acceptable in light of the benefits to be derived from the conduct and results of the research [28, 35]. This decision should be confirmed by people familiar with other studies.

INDEPENDENT REVIEW

To minimize concerns with regard to researchers' conflicts of interest and to ensure public accountability, independent ethical review of all clinical research protocols is necessary [25]. In addition to institutional review board or research ethics committee review, other regulatory approvals may be necessary for some types of research.

In multinational research, there is a special need for transparency [28]. Transparency enhances accountability by assuring the public that the research is not exploitative. Whether supplementary reviews by local community councils, nongovernmental organizations involved with the community, international health organizations, or ministries of health are appropriate depends on the nature of the collaborative partnership. If such reviews are in disagreement, it is important to clarify the nature of the disagreement. In many cases, disagreement reflects different ways of balancing various principles and benchmarks or the appropriateness of different ways of fulfilling them—that is, not whether the ethical requirements are met, but how they are met [49]. Conflicts may also arise because of different guidelines or regulatory requirements, which themselves may not have good ethical justification or may be insensitive to particular cultural or social circumstances in developing countries [14, 50]. Only rarely are there fundamental disagreements about whether ethical principles and benchmarks are met. Unfortunately, there is no widely accepted procedure for adjudicating such conflicts. In practice, the requirements specified by the review board in the sponsor's country are often determinative, which contravenes the principle of collaborative partnership [51].

Finally, review must be independent and competent [25]. Review bodies may have conflicts because of relationships with the researchers or pressures from those promoting the research. Supplementary training in ethics for review bodies may be necessary.

INFORMED CONSENT

Individual informed consent has been recognized as a principle of ethical clinical research for more than a century [52, 53]. Differences in language, social traditions, and practices make the process of informed consent in developing countries complex and suggest 5 benchmarks for evaluating informed consent. First, the local community should help to establish recruitment procedures and incentives for participants that are consistent with cultural, political, and social practices. In some communities, compensation for participation in research may be expected, whereas, in others, it may be considered offensive. The appropriate form and level of compensation depends on the local economic and social context. Although concerns about inducement are frequently raised, high potential social value and a favorable risk-benefit ratio dispel these concerns [54, 55]. Indeed, focusing on undue inducement could reduce compensation and some of the benefits for subjects and host communities. Paradoxically, balancing fair compensation and undue inducement may result in less compensation for members of impoverished communities.

Second, disclosure of information should be sensitive to the local context. It should be done using the local language, culturally appropriate idioms, and analogies that the prospective participants can understand. This obviously entails a need for collaborative partnership.

Third, "spheres of consent," ranging from village elders to leaders of the extended family or heads of households, may be required before researchers can invite individual participation [35]. With few exceptions, such as emergency research, it is unacceptable to supplant individual consent of adults by family or community consent [35, 56]. The family or community only gives permission to invite individuals to participate.

Fourth, researchers should use consent procedures that are acceptable within the local community, while ensuring that an independent observer could verify volun-

tary participation by the individuals. For instance, US regulations requiring a written signature are culturally insensitive in many cases [53, 57]. Appropriate alternative procedures for documenting informed consent might include tape recordings or written documentation of verbal consent.

Fifth, special attention must be given to ensure that individuals are aware of their right to and actually are free to refuse to participate or withdraw from research [58]. To obviate familial or community coercion or retribution, steps such as prorating compensation and other benefits related to the research should be taken.

RESPECT FOR RECRUITED PARTICIPANTS AND STUDY COMMUNITIES

The ethical conduct of clinical research does not end when informed consent is obtained [25]. Researchers have ongoing obligations to participants, former participants, and the host community. First, an essential obligation is to develop and implement procedures to maintain the confidentiality of information collected. Such procedures might include interviewing participants outside, where they cannot be overheard, or permitting participants to not receive HIV test results. In addition, it is important to alert participants that, despite researchers' best efforts, there is no guarantee of absolute confidentiality.

Second, respect for participants includes informing them of their right to withdraw [58]. Third, participants and the community should be informed when new information, such as a newly discovered risk, arises during the course of research. Fourth, exacerbations of the disease being studied, adverse events from research interventions, and health problems that arise unrelated to the disease being studied may require care. Researchers should specify a strategy for monitoring the progress of the disease, adverse events from the intervention, any untoward changes in health, what steps will be

taken to provide care under these circumstances, and what compensation there will be for research-related injuries.

One problematic area with regard to research in developing countries is the responsibility of researchers for participants' health problems that are unrelated to the condition being studied. In developed countries, researchers commonly refer participants to the existing health-care system, notwithstanding deficiencies in insurance coverage and provision of care. In developing countries, geography and scarce resources may make treatment for diseases unrelated to the research unavailable. Currently, there are no clearly defined parameters to guide researchers in these situations. Clinical research is not clinical care [59]. Researchers are not obligated to remedy the deficits of a country's health-care system or to ensure that all participants' medical ailments are given appropriate care. Conversely, researchers cannot ignore concomitant health problems of their participants. At a minimum, researchers should ensure access to local health services or alternatives of equal quality and meet national care guidelines when specified, such as for childhood immunizations. In some cases, researchers may provide interventions for unrelated health conditions that are superior to those locally available, especially if they are relatively easy and economical to provide under local conditions. It is important that plans for provision of care of unrelated health conditions be developed as part of the collaborative partnership between researchers, the host community, and makers of health policies.

What medical services should be provided to research participants after completion of the study? Some have argued that interventions proven to be beneficial to participants during a study should be made available to them at the completion of the study [13, 60]. Continued access to experimental medications is one way in which subjects may benefit from research participation [28]. However, participation in research does not necessarily entitle

subjects to continue receiving treatment, nor does it obligate investigators to provide continued treatment; to do so would be to confuse research with clinical care.

Finally, researchers should develop explicit strategies to inform participants and host communities of the results of the research [35]. Having participated in the research and assumed risks, the participants and host community have a right to know what was found and its implications for public health and health-care policies.

APPLYING THE PRINCIPLES AND BENCHMARKS

Together, these principles and benchmarks constitute a systematic framework that specifies core practical considerations necessary to ethically justify research in developing countries. It can probably be applied to all research, regardless of setting or sponsorship. This is a first attempt to specify a comprehensive list of benchmarks. Application to actual research studies may suggest refinement or the need for additional benchmarks [30, 41].

Importantly, differences in health, economic, social, and cultural aspects of a research setting will affect application of the framework—specifically, how much “weight or priority [is] given to different benchmarks” [30, page 740]. Depending on a study's objectives and context, particular benchmarks will be given greater weight than others. Such balancing is inevitable whenever there are multiple ethical considerations [32–34]. This does not mean that the principles and benchmarks are relativistic; rather, it means that the adaptation and balancing of universal principles are relative to risk, resources, social practices, and similar circumstances.

Moral arguments take place in context, and they therefore depend at least implicitly on matters of fact, estimates of risk, suppositions about feasibility, and beliefs about human nature and social processes.... Even those who rely on what they regard as universal moral principles do not presume

that their practical conclusions are independent of reliable facts and plausible assumptions about particular societies. The arguments begin from where we are, and appeal to those with whom we now live. This is why moral relativism is seldom as important an issue in practical as it is in theoretical ethics. [6], page 14–15]

OBJECTIONS CONSIDERED

The first objection to consider is that this framework is overwhelming, erecting barriers to research in developing countries. However, it does not add ethical requirements; rather, it provides an explicit and systematic delineation of steps already being taken by conscientious researchers in developing countries.

Second, it may be claimed that these principles and benchmarks are obvious and do not add to existing guidance. Indeed, the principles are distilled and made coherent from widely accepted guidance, including the Nuremberg Code [22], the Declaration of Helsinki [13], the Belmont Report [24], or the US "Common Rule" [58]. The benchmarks provide more-specific and more-practical guidance: a set of measures that can serve as a reminder and common reference for all those planning, conducting, and evaluating research. Such obviousness constitutes a virtue. Agreement on the benchmarks would indicate that consensus on the broad principles could be extended to ever more-specific and more-substantive aspects of the ethical framework, narrowing the disagreement that Macklin justifiably laments [29].

Third, disagreement is inevitable [29]. We agree. Consideration of multiple ethical principles and benchmarks simultaneously is likely to create reasonable disagreement [32–34]. However, these benchmarks can both narrow the disagreements and make them less ethically worrisome. Ignoring basic principles or rejecting the benchmarks in designing and conducting a research study could render a study unethical. Conversely, accepting the principles and

benchmarks, yet disagreeing about how to balance them in a particular case, highlights the intricacies of ethical judgments entailing multiple considerations [61]. Disagreement on the balancing of the various benchmarks does not necessarily make one assessment ethical and the other unethical. Rather, it may reflect different but legitimate ways of resolving competing ethical claims. In fact, this framework can help narrow disagreements and elucidate the different underlying views. Ultimately, in the effort to ensure that research is conducted ethically, a thoughtful process of balancing ethical considerations can be as important as any particular judgment.

Acknowledgments

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Appendix F – Fair Benefits Framework

Emanuel, E.J. and Participants in the 2001 Conference on Ethical Aspects of Research in Developing Countries, Excerpt from, *Addressing Exploitation: Reasonable Availability versus Fair Benefits*, In Hawkins, J.S. & Emanuel, E.J. (Eds.). (2008.) *Exploitation and Developing Countries: The Ethics of Clinical Research*, Princeton, New Jersey: Princeton University Press, p. 286-310, Excerpt pages 298-303.

The Fair Benefits Framework

Ethically, targeted populations in developing countries must benefit from the conduct and/or results of clinical research performed in their communities. While reasonable availability is one way to provide benefits to a population, it is not the only way. Hence, it is not a necessary condition for ethical research in developing countries and should not be imposed without affirmation by the developing countries themselves.

As an alternative to reasonable availability this group proposes the fair benefits framework (table 2, columns 1 and 2).²⁹

The fair benefits framework supplements the usual conditions for the ethical conduct of research trials, such as independent review by an institutional review board or research ethics committee and individual informed consent.³⁰ In particular, it relies on three background principles that are widely accepted as requirements for ethical research. First, the research should have social value by addressing a health problem of the developing country population. Second, fair subject selection ensures that the scientific objectives of the research itself, not poverty or vulnerability, provide a strong justification for conducting the research in a specific population. For instance, the population may have a high incidence of the disease being studied or transmission rates of infection necessary to evaluate a vaccine. Third, the research must have a favorable risk-benefit ratio, in which benefits to participants outweigh the risks, or the net risks are acceptably low.

The fair benefits framework adds three principles that are specified by fourteen benchmarks to these widely accepted principles (table 2, columns 1 and 2).

Principle 1: Fair Benefits

There should be a comprehensive delineation of tangible benefits to the research participants and the population from the conduct and results of the research. These benefits can be of three types: (1) benefits to research participants during the research, (2) benefits to the population during the research, or (3) benefits to the population after completion of the research (table 2, column 2). It is not necessary to provide each of these types of benefits; the ethical imperative based on the conception of exploitation is for a fair level of benefits. Indeed, it would seem fair that as the burdens and risks of the research increase, the benefits should also increase. Similarly, as the benefits to the sponsors, researchers, and others outside the population increase, the benefits to the host population should increase.

Importantly, because the aim of the fair benefits framework is to avoid exploitation, the population at risk for exploitation from the research

TABLE 2
THE FAIR BENEFITS FRAMEWORK

<i>principles</i>	<i>Benchmarks</i>	<i>Hepatitis A Vaccine Thailand</i>
air benefits	<ul style="list-style-type: none"> • Benefits to participants during the research 1. Health improvement: There are health services essential to the conduct of the research that improve the health of the participants. 2. Collateral health services: There are health services beyond those essential to the conduct of the research provided to the participants. 	<p>Hepatitis A vaccine provided to all participants.</p> <p>Hepatitis B vaccine for all participants; surveillance and triage of illnesses.</p>
	<ul style="list-style-type: none"> • Benefits to population during the research 3. Collateral health services: There are additional health care services provided to the population. 4. Public health measures: There are additional public health measures provided to the population. 5. Employment and economic activity: There are jobs in the research project for the local population and spending that stimulates the local economy. 	<p>Hepatitis B vaccine for health care workers and teachers; unlimited disposable syringes and needles.</p> <p>Improved refrigeration at rural health stations; FM wireless network for rural health stations; correction of hygiene deficiencies in schools, report on epidemiology of childhood mortality.</p> <p>Some employment of research personnel.</p>
	<ul style="list-style-type: none"> • Benefits to population after the research 6. Availability of the intervention: If proven effective, the intervention should be made available to the population. 7. Capacity development: There is capacity development through improvements in health care physical infrastructure, training of health care and research personnel, and/or training of health personnel in research ethics. 	<p>Registration of hepatitis A vaccine and sales, using tiered pricing, on the private market.</p> <p>Limited training and preparation for vaccine trials.</p>

TABLE 2 (continued)

<i>Principles</i>	<i>Benchmarks</i>	<i>Hepatitis A Vaccine Thailand</i>
	<ul style="list-style-type: none"> 8. Public health measures: There are additional public health measures provided to the population. 9. Long-term collaboration: The particular research trial is part of a long-term research collaboration with the population. 10. Financial rewards: There is a plan to share fairly with the population the financial rewards and/or intellectual property rights related to the intervention being evaluated. 	<p>Identification of possible mechanisms to reduce motor vehicle accidents.</p> <p>Part of a long-term collaboration and may have facilitated securing HIV vaccine trial.</p> <p>No sharing of financial rewards.</p>
Collaborative partnership	<ul style="list-style-type: none"> 11. Free, uncoerced decision making: The population is capable of making a free decision, there are no threats, and the population can refuse participation in the research. 12. Population support: After receiving an explanation of—and understanding—the nature of the research trial, the risks and benefits to individual subjects, and benefits to the population, the population targeted for the research voluntarily decides it wants the research to proceed. 	<p>Rejecting the trial was possible.</p> <p>Consultation with the provincial population, government, and teachers; approval by Ministry of Public Health.</p>
Transparency	<ul style="list-style-type: none"> 13. Central repository of benefits agreements: An independent body creates a publicly accessible repository of all formal and informal benefits agreements. 14. Community consultation: Forums with populations that may be invited to participate in research, informing them about previous benefits agreements. 	<p>No repository existed, but the absence of reasonable availability and the provision of benefits were publicly discussed with the government and provincial population.</p>

study is the relevant group to receive benefits and determine their fairness. Indeed, determination of whether the distribution of benefits is fair depends on the level of benefits received by those members of the community who actually participate in the research, for it is they who bear the burdens of the interaction. However, each benefit of research does not have to accrue directly to research participants but could benefit the entire community. For instance, capacity development or enhanced training in ethics review could be provided to the community. The important determination is how much the participants will benefit from these measures. In addition, the community will likely bear some burdens and impositions of the research because its health care personnel are recruited to staff the research teams, and its physical facilities and social networks are utilized to conduct the study. Thus, to avoid exploitation, consideration of the benefits for the larger community may also be required. However, analysis of exploitation as inhering in micro-level transactions makes clear that there is no justification for including an entire region or every citizen of a country in the distribution of benefits and decision making, unless the whole region or country is involved in bearing the burdens of the research study.

Principle 2: Collaborative Partnership

The population being asked to enroll determines whether a particular array of benefits is sufficient and fair. Currently, there is no shared international standard of fairness; reasonable people disagree.³¹ More important, only the host population can determine the value of the benefits for itself. Outsiders are likely to be poorly informed about the health, social, and economic context in which the research is being conducted, and are unlikely to fully appreciate the importance of the proposed benefits to the population. Furthermore, the population's choice to participate must be free and uncoerced; refusing to participate in the research study must be a realistic option. While there can be controversy about who speaks for the population being asked to enroll, this is a problem that is not unique to the fair benefits framework. Certainly, even—or especially—in democratic processes unanimity of decisions cannot be the standard; disagreement is inherent. But how consensus is determined in the ab-

sence of an electoral-type process is a complex question in democratic theory beyond the scope of this chapter.

Principle 3: Transparency

Fairness is relative, determined by comparison with similar interactions. Therefore, transparency—like the full information requirement for ideal market transactions—allows comparisons with similar transactions. A population in a developing country is likely to be at a distinct disadvantage relative to the developed country sponsors in determining whether a proposed level of benefits is fair. To address these concerns, a publicly accessible repository of all benefits agreements should be established and operated by an independent body, such as the World Health Organization. A central repository permits independent assessment of the fairness of benefits agreements by populations, researchers, governments, and others, such as nongovernmental organizations. There could also be a series of community consultations to make populations in developing countries aware of the terms of benefits agreements in other research projects. This will facilitate the development of “case law” standards of fairness that evolve out of a number of agreements.

Together with the three background conditions, these three new principles of the fair benefits framework ensure that (1) the population has been selected for good scientific reasons; (2) the research poses few net risks to the research participants; (3) there are sufficient and long-lasting benefits to the population; (4) the population is not subject to a coercive choice; (5) the population freely determines whether to participate and whether the level of benefits is fair given the risks of the research; and (6) the repository offers the opportunity for comparative assessments of the fairness of the benefit agreements.

Appendix G – Translation Attestation Form

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 Harvard School of Public Health
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Translation Attestation Form

Instructions: The Principal Investigator is responsible for ensuring that HSPH IRB-approved study documents, e.g., recruitment materials and consent forms, are accurately translated into a language understandable to study participants. If any study documents will be administered in languages other than English, the Principal Investigator must:

- Submit this form with the Initial Application for Human Research.
- Submit this form if, as part of a study modification, there is a request to add new study documents that will be translated.
- Ensure that all translated documents are approved by the local IRB/Ethics Committee (EC), prior to their use in the field.
- Submit the locally-approved, translated documents to the HSPH IRB as soon as they become available.

A. PROTOCOL INFORMATION				
<input type="checkbox"/> Initial Review <input type="checkbox"/> Modification Request (to add new documents)				
Protocol Number:				
Protocol Title				
Principal Investigator / Degree(s):		/		
B. LIST OF DOCUMENTS TO BE TRANSLATED				
Document Name	Name(s) of Local Reviewing IRB/Ethics Committee	Translated Language(s)	Person Preparing Translation(s)	Name of Translator
			<input type="checkbox"/> HSPH PI <input type="checkbox"/> Local Investigator <input type="checkbox"/> Certified Translator <input type="checkbox"/> Other, Specify:	
			<input type="checkbox"/> HSPH PI <input type="checkbox"/> Local Investigator <input type="checkbox"/> Certified Translator <input type="checkbox"/> Other, Specify:	
			<input type="checkbox"/> HSPH PI <input type="checkbox"/> Local Investigator <input type="checkbox"/> Certified Translator <input type="checkbox"/> Other, Specify:	
			<input type="checkbox"/> HSPH PI <input type="checkbox"/> Local Investigator <input type="checkbox"/> Certified Translator <input type="checkbox"/> Other, Specify:	
C. PRINCIPAL INVESTIGATOR ATTESTATION AND SIGNATURE				
By signing this form, I attest that I understand my responsibility as Principal Investigator to ensure that IRB-approved study documents, e.g., recruitment materials and consent forms, are accurately translated in a language understandable to study participants.				
Principal Investigator's Signature _____			Date _____	

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D. TRANSLATOR SIGNATURE

By signing this form, I confirm that translations of the documents listed above will be accurate and complete. (Note: If the Principal Investigator has performed the translations, please contact the IRB Review Specialist assigned to your department for further guidance. Contact information is available at: <http://www.hsph.harvard.edu/research/human-research-administration/department-assignments/>)

Translator's Signature

Date