Chapter 6: International Clinical Research

International clinical research is different from domestic research in developed countries because of the differing cultures of the researchers and the prospective subjects as well as because of their differing understandings of what will happen and why. It's easy to see why cultures with a daily fight for survival might find the issues of concern to the investigators quite foreign and puzzling. Yet, research must be done in low resource countries to deal with their medical problems, which differ from those of the developed world. Issues for the investigative team include:

A. Underlying conditions

1. **Governments are less stable, insurgency may impair studies**
2. **Protections for citizens are weak**
3. **Disease portfolio, nutritional state, health care belief systems are different in developing countries and these differ from locale to locale**
4. **Very rudimentary health care systems making it unlikely that study drugs will be affordable by the general population**
5. **Serious logistical problems sometimes encountered in carrying out research, power, transportation, communication.**

B. Approval and Monitoring Issues

1. **Requires an approved local IRB as well as an IRB from the sponsoring institution to approve the protocol and there are numerous misunderstandings and conflicts requiring a rational adjudication process. The IRBs and sponsors must agree on much more than in a developed country study.**
   It is here that paternalism conflicts with national self-determination. There is conflict over whether controls should receive the developed nation standard of treatment rather than what would normally be available to them in their own country.
2. **Studies require an effective Data and Safety Monitoring Board to adjudicate problems as well as to monitor the progress of the study but that might not be so easy to arrange.**
3. **Adverse medical, social, and psychological events are not predictable but must be dealt with. Studies need a Standard Operating Procedure (SOP) for dealing with the unexpected.**

C. Study population issues

1. **There are many vulnerable populations who might be study subjects especially with high illiteracy, limited exposure to the concepts of western medicine and to the idea of research.**

Major cultural differences must be understood sufficiently to avoid harm

2. **There is often a requirement that the community or communities of the individual participants be involved in the research process during development as well as during execution.**
3. **Investigators must avoid coercion through bribery, but food supplies, health care, etc. may be the equivalent of bribes in certain cultures.**
4. **The consent process must be informational, understood, and voluntary and that's often difficult. Testing for comprehension is very helpful. Also the consent process must be repeatedly reiterated during the course of the study. It's worthwhile for the entire community to understand the research.**
5. **There may be joint consent (with spouse) but the subject needs to receive health information privately and decide whether or how to present it to the other party.**
6. **Development of health information about individuals must be dealt with exceedingly carefully as it can easily lead to stigmatization of individuals or of groups.**

D. Structural Issues

1. **Obtaining and sustaining privacy and confidentiality may be a serious problem. Physical privacy for exams and questioning may be hard to find. Secure storage of data may be problematic. In certain cultures, the study personnel may be subject to intimidation to give up private information. Privacy extends to recruiting as well as to execution.**
2. **Investigators must ensure that scarce health personnel and facilities are not usurped by a study to the detriment of local health care.**
3. **Processing and transport of biological specimens may be problematic, especially if transported out of the country.**
4. **It is highly desirable to utilize local personnel to help plan and manage the study and often this means a number of meetings and training sessions**
5. **Often there is a requirement for a long-term continuation of care or technical support to the community but the degree and duration remain negotiable and if adverse events occur, the extent of required support might be extremely contentious. Community demands may not be affordable.**

E. Epidemiological and Social Science Research

1. **These create new kinds of risks for social groups as well as individuals, including stigma, denial of access to health care, etc.**

2. **In the epidemiological setting, ascertainment of the condition for the group may compete with privacy for the individual. The issue of societal need versus privacy commonly occurs with public health.**
2. **Clinical trials are more fraught with difficulty because of local issues. These include**

    Ascertainment bias in design
    Bias in reporting
    Inappropriate access to data
    Adverse event reporting
    Appropriate monitoring
    Monitoring of Phase 1 and 2 trials

3. **Protection of subjects. This includes:**

    a) Assessing risks and benefits of treatments and of controls in the field
    b) Estimation of equipoise, individual and societal
    c) Data and safety monitoring in the field
    d) Social risks and psychological risks as they develop in the field. These may not be anticipated.
    e) Privacy and confidentiality in diverse communities with curious and meddling officials
    f) Therapeutic misconception of naïve subjects who don't understand the idea of research.

Cases: Chapter 6

Case: The Tawa

A previously unknown tribe in Papua-New Guinea, the Tawa was found to have an average adult height of 36 inches despite adequate nutrition. After the first report of discovery, the research community expressed an intense interest in studying the Tawa genetically, physiologically, sociologically, and psychologically as well as to determine whether they can be helped to attain greater height by medication.

Similarly, the media developed a most intense interest in televising the tribe to produce news stories and documentaries.

Access to these people was put under control of Papua-New Guinea Interior Minister who happened to be a physician educated in Australia. She wanted very much to do the right thing and was fearful that without careful control, chaos would ensue. An influx of Westerners however, would be a great shot in the arm to Papua New Guinea's weak economy.

She decides to hire you as the reigning expert to advise her and the tribe. You make a trip with your interpreter by jeep, donkey, and foot, mainly up hill and make acquaintance with the 80 members of the tribe.

You are sure that the tribe has a selective defect in the growth hormone-IGF_1 axis that will be very interesting, and that the tribe's isolation for many generations makes genomic study very interesting. It would also be valuable to use the opportunity of drawing blood to investigate their cardiovascular risk factors and susceptibility to infections.

In fact, the number of valuable studies immediately conceivable was enormous.

Questions:

1. **Is it ethical to conduct research on the Tawa? Elaborate on the background issues that will help you to decide?**
2. **The concepts of writing, blood drawing, research and questionnaires are unknown to the Tawa. Although they have language, it is limited to 500 words or so and does not include many specifics. How are you going to explain to them what research and genetic research are?**
3. **The tribe is a vulnerable population. Is there a way of getting a surrogate to stand for them in understanding planned research?**
4. **What will you write in your report to the Interior Minister?**

CASE: Research with Indigenous Tribe

Deep in the Brazilian jungle the Ogura tribe retains its ancient culture of nakedness, hunting, including the cannibalization of males from other villages and capturing females and children, as well as gathering edible vegetation and fishing in adjacent streams. The Ogura are big and strapping and seem to have a lot of children. However, very few Ogura can be found who appear older than around 50 years of age.

The Brazilian government has made extensive contact with indigenous cultures and has agents and translators who visit regularly and are accepted by the tribe. The government is concerned that tree poachers are destroying the jungle habitat for indigenous cultures. The Ogura, using lightning raids, have killed a number of poachers and, to date, have preserved their environment.

You, as a great public health and genetic researcher have been invited by the government to initiate genetic, anthropological and public health research into the tribe in hopes of helping them survive, either in their own environment or in the modern world.

You see this as a great but ethically challenging opportunity. You schedule a visit to the Ogura with the agent and translator.

Questions:

1. What issues would you like to cover in your visit?

2. The desired information includes the blood of as many members of the tribe as possible to do genome analysis and determine whether there are clinical reasons for their apparent short life spans. What ethical issues arise as you consider how to do this?

3. How will you go about conducting research on this population?

Bibliography

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This is a discussion of the problems involved in developing medical technology, including drugs, in India. The authors consider issues with the research and adaptation of Western concepts of ethical clinical research. They also discuss political influences on research decisions including the battle between spending for prestige and spending to relieve the world problems.

Levine, R. (2000). "Some Recent Developments in the International Guidelines on the Ethics of Researching Involving Human Subjects." Ann NY Acad Sci November(918): 170-8.

The author carefully reviews the most controversial elements of the Declaration of Helsinki after strong wording had been inserted in relation to use of placebos. He argues both that the concepts of therapeutic vs. non-therapeutic studies and the prohibition of placebo use when effective agents exist are misleading and sometimes embarrassing in their implications.

Marshall, P. (2005). "Human Rights, Cultural Pluralism, and International Health Research." Theoretical Medicine and Bioethics **26**(6): 529.

This thoughtful paper deals with the ethical obligations to consider human rights, socioeconomic, and political issues in conducting international health research, especially in resource-poor countries. Not only does there have to be a great deal of community input -- to the point of partnership, but physical resources and know-how have to be part of the package so that the community receives continued benefit from the research. One might consider some parts of the US as similarly deprived with similar needs. http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1007/s11017-005-2199-5

Cooley, D. R. (2001). "Distributive Justice and Clinical Trials in the Third World." Theoretical Medicine and Bioethics **22**(3): 151.

This long philosophical paper addresses the claim that in international research in resource-poor countries, those who are non-participants are exploited. They, it is argued, are denied access to reasonable availability of the products of the research. This aspect of distributive justice is argued against in this paper. http://www.springerlink.com/openurl.asp?genre=article&id=doi:10.1023/A:1011452716028

Molyneux, C. S., D. R. Wassenaar, et al. (2005). "'Even if they ask you to stand by a tree all day, you will have to do it (laughter).' Community voices on the notion and practice of informed consent for biomedical research in developing countries." Social Science & Medicine **61**(2): 443.

This extremely interesting report was directed at the question of informed consent in a resource-poor area of Kenya where much research was done. They found, in asking who should be asked to give

consent that the answer was muddled by the persistent belief that the research was clinical care. This should be a lesson to those dwelling on the nuances of informed consent in such settings.
http://www.sciencedirect.com/science/article/B6VBF-4FFN4N5-1/2/b7d785f694ea7703bdca485d4670769e

Molyneux, C. S., N. Peshu, et al. (2004). "Understanding of informed consent in a low-income setting: three case studies from the Kenyan coast." Social Science & Medicine **59**(12): 2547.

This really useful paper elaborates with specificity the issues surrounding acceptance of research activities in a very resource-poor environment in Kenya. The limited vocabulary to try to explain research leaves the participants trying to explain why it is that the researchers are doing what they do. There are exaggerated concepts of what such things as blood drawing can do to help individuals in studies designed to help populations. Very worthwhile.
http://www.sciencedirect.com/science/article/B6VBF-4CKFGMR-3/2/c2f00be4516113128f7ec7f2c11f9a17

Benatar, S. (2002). "Reflections and recommendations on research ethics in developing countries." Soc Sci Med **54**(7): 1131-41.

Benatar, one of the grand elders of international ethics, discusses broad responsibilities for ethics review committees beyond informed consent and risk-benefit ratios. He believes that these committees should communicate at the community level, monitor research, and act to enhance the research capacity of each country by entering the political domain. These very perceptive remarks provoke considerable reflection.

Upvall, M. and S. Hashwani (2001). "Negotiating the informed-consent process in developing countries: a comparison of Swaziland and Pakistan." Int Nurs Rev **48**(3): 188-92.

This study describes and analyzes the issues in protecting the rights of research participants in developing countries with emphasis on Pakistan and Swaziland. The main issues related to gatekeepers at all levels who were either eager to exercise control or to protect their positions. It emphasizes just how much prelim work had to be done before research could commence.
http://www.blackwell-synergy.com/doi/abs/10.1046/j.1466-7657.2001.00063.x

Emanuel, E., W. D, et al. (2004). "What makes clinical research in developing countries ethical? The benchmarks of ethical research." J Infect Dis **189**(5): 930-7.

The authors provide a comprehensive set of guidelines to investigators engaged in or considering research in developing countries. In these guidelines they elaborate in the communities (social) concerns in clinical research and the avoidance of exploitation using a 33 point table. This is a real contribution.
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This is a description of the research ethics committee status of the 46 countries in Sub-Saharan Africa that are related to WHO. IT indicates that only 2/3 have a research ethics committee (as of 2001) although 80% hard some sort of review process. They propose that even the poorest country should set up a review system.
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This empirical study investigates the reality of clinical research carried out in developing countries sometimes in collaboration with US investigators. They found that many of the studies being carried out by over 600 investigators had no IRB approval and that many of the recommendations of the US National Bioethics Advisory Commission were not in effect for example, language-appropriate consent forms.
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Kottow, M. H. (2003). "The Vulnerable and the Susceptible." Bioethics **17**(5-6): 460-471.

The author distinguishes the word vulnerable -- the underlying state of mankind requiring government to keep us from each other's throats; and susceptible -- a state of defective health that makes some of us ethically entitled to help others. Applied to research on humans, this applies to subjects from developing countries.
http://www.blackwell-synergy.com/doi/abs/10.1111/1467-8519.00361

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The authors present their experiences and raise questions about the meaning of informed consent and how the model of implementation could be changed.
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A unique survey conducted under the auspices of the NBAC studying researchers from developed countries perspectives on oversight of research in developing countries. They developed an instrument using focus groups. They identified appropriate researchers and got a 47% response rate. The results indicated beliefs of the investigators regarding the oversight of studies they were conducting in a number of domains. Well worth reading.

Dickens, B. M. and R. J. Cook (2003). "Challenges Of Ethical Research In Resource-Poor Settings." International Journal of Gynecology & Obstetrics **80**(1): 79.

This study focuses on reproductive studies of women from developing countries. It details barriers that are institutional, issues with informed consent, use of placebos, problems with ethics review committees, etc.
http://www.sciencedirect.com/science/article/B6T7M-47MNYN7-G/2/8fb17bab203b70338b01aeb84eb01186

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This brief paper reviews the controversy surrounding the limitations on clinical research resulting from the requirement of the Declaration of Helsinki year 2000 version's absolute requirement for the best standard therapy in controls of therapeutic trials. The authors point out that other groups give investigators more experimental design options. So, the debate over treatment options in studies in developing countries persists.
http://jme.bmjjournals.com/cgi/content/full/30/2/190