POTENTIAL EXPOSURE TO LIABILITY OF INVESTIGATORS PERFORMING CLINICAL RESEARCH IN DEVELOPING NATIONS

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Every clinical investigator works with some risk of liability associated with investigations associated with human subjects. In fact, field investigators whose research touches the environment, also share a liability exposure for environmental damage. International clinical trials, particularly those in developing countries have a long history of relative insulation from liability risk. Recent developments conspire to elevate this level of risk.

The potential for being sued varies remarkably country by country but it always remains a possibility. In the United States, anyone can be sued at any time for no more than the cost of a filing fee. It is winning the suit not filing that counts never-the-less the mere act of being sued can be damaging. Frivolous suites are discouraged and filed at some risk. An international setting magnifies the opportunities through issues of choice of law and choice of a venue.

A hypothetical may help in the explanation of the evolving risks and options. Assume a drug trial in a developing nation, Z. A US government grant supports this study. The grant is to a major research university in the US. The principal investigator is an employed faculty member at that University. There are co-investigators at a hospital in Z. The drug is to be tested against soil transmitted helminths. Institutional review committee approval is forthcoming from the US institution as is approval from the Ministry of Health in Z. With headman, school principal and mothers consent school children are surveyed and double blind a drug or placebo is administered. Simple consent is obtained without mention of side effects. An untoward but on review of prior human research and animal data not to be unexpected side effect occurs. Children are injured. The results are published.

This is a plaintiff attorney's dream. There are multiple clients permitting class action. Damages have occurred. The investigators knew or should have known. The possibility for punitive damages is open. Consent is arguably defective. The University is a deep pocket. The drug manufacturer an even deeper pocket. The claim might include simple negligence, medical malpractice, battery, and product liability. The problem is that all events occurred in Z.

In Z the risk of liability would be determined by the statute, code or common law of the country. The treatment of personal injury and particularly malpractice liability varies widely among nations particularly in civil law jurisdictions. Jurisdiction over the investigator who has returned to the US may not be readily established. The University and the drug company may be even further removed. This all depends on the nature and existence of a suitable long arm statute in Z. A judgment rendered at a trial in Z might not receive full faith and credit when presented at a US court. All of this offers substantial insulation from possible suit. As an example the interest by the plaintiff bar in the US in clients from Bopal dimmed when it became clear that litigation would occur in India and not the United States.

Suit could be brought in domestic (US) courts, either state or federal, however aggressive defense would move to have the case quashed with the most likely grounds being *forum non conveniens*. US courts look with suspicion and some disfavor on attempts to take advantage of more generous plaintiff awards common in US courts if suitable legal forums exist in the country where the incident occurred. A suit in the US might stand a chance if Z lacked a reasonable forum because of war or anarchy.

If the suit were to be brought in the US the nature of the risk, better called possible causes of action might include:

a. Negligent malpractice
b. Medical malpractice
c. Product liability
d. Battery by violation of informed consent
e. Statutory or code violation such as practice of medicine without a license in Z.

Exposure to the risk or who gets sued include:

a. Investigator
b. The investigators employer (institution) under *respondeat superior*
c. The pharmaceutical manufacturing company
d. The granting agency

e. Any collaborating investigators including in Z
f. Any collaborating institutions in Z.

A third venue for suit has opened in Europe with the establishment of The European Court of Human Rights. This court permits an ordinary citizen to file against a member state where the issue involves a violation of human rights. There are currently 40 member nations in Europe. Given the expansion of multinational funding of projects it is a potential, yet small risk. The addressable violations are limited to human rights.

A fourth venue is in Belgium. There, by statute the country has opened its court system to cases where there are allegations of crimes against humanity committed anywhere in the world but with the requirement that the accused visits Belgium. Currently a group of Palestinian survivors of a 1982 raid has filed against Ariel Sharon, the then Defense Minister. Past and pending cases include Rwandans involved in genocide against Tutsi in 1994, complaints against the President and former military ruler of the Ivory Coast, the dictator of Chad and the Interior Minister of Morocco. This has become a politically volatile issue in Belgium.

This leads to the issue of human rights violation as a cause of action. In August 1947 the Nuremberg Code was formulated. It and its progeny, the International Code of Medical Ethics of the World Medical Association (1949), the Declaration of Helsinki of the World Medical Association (1964) amended in 1975, 1983, 1989, 1996, and 2000 (World Medical Association, 2000) and the 1971 US Guidelines on Human Experimentation, subsequently amended, all collectively recognize the autonomy of the individual in regards to participation in research on human subjects or more simply the requirement for individual informed consent.

In 1948 the United Nations General Assembly adopted the Universal Declaration of Human Rights. Dignity, discrimination, compromise of medical independence and unethical research practices are all touched in the Universal Declaration. Here, environmental protection figures as well. Environmental protection and the protection of human subjects involved in research, particularly the issue of informed consent, have through declaration or treaty become the law of nations or international law.

Few of us would anticipate ethical challenge of carefully done trials that rigidly follow protocols approved by thoughtful Institutional Review Boards yet over the last decade this has been a regular occurrence. In 1988 The New England Journal of Medicine highlighted this problem in a Sounding Board article by Barry, *Ethical Considerations of Human Investigation in Developing Countries, The AIDs Dilemma* (Barry, 1988). The Journal of the American Medical Association published *Ethical Behavioral and Social Aspects of HIV Vaccine Trials in Developing Countries* (Lurie *et al*, 1994). The New England Journal of Medicine returned to this issue with *Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries* (Lurie and Wolfe, 1997) and *Ethical Issues in Studies in Thailand of the Vertical Transmission of HIV* (Phanuphak, 1998). While study design has come in for its share of criticism, informed consent has almost always been an issue. These articles provoked much editorial comment and correspondence with no clear answer to the requirements for ethical behavior.

Lest one think this is an AIDs issue I would point out that in the last decade ethical challenges have risen over photodynamic therapy for bladder cancer in China, *Echinococcus* diagnosis in North Africa, therapy for *Ascaris* in East Africa, analgesic testing in Thailand and the use of placebo controls in general. There has been recent international pronouncement raising an ethical concern about the use of placebo in drug testing where there is extant an alternative drug of proven utility ((World Medical Association, 2000). The use of placebo rather than alternative drug in the test arguably rises to the level of a human rights violation. Again although there are other issues informed consent is a regular focus of criticism. By highlighting these controversies I am in no way attempting to favor one or the other position. I use it only to illustrate that there is an arguable ethical and scientific controversy and informed consent is at its core. Where there is an arguable controversy, litigation and liability follow.

Remember issues of consent touch the laws of nations. A tort claim by an alien against an individual or entity in the United States based on violation of the laws of nations may be brought in the US through the Alien Tort Claims Act of 1789. The first Congress of the United States met in New York in 1789. George Washington was president, John Adams was vice president and Fredrick Augustas Mulenberg speaker of the house. It set the salary of the President, established executive departments including War and State and passed the enabling legislation for the Federal Judiciary. The legislation regarding the judiciary passed on September 24, 1789, was in Chapter 20. Section 9 was devoted to the jurisdiction of the District Courts. It said:

That the district courts shall have, exclusively of the courts of the several States, cognizance of all crimes and offenses that shall be cognizable under the authority of the United States, committed within their respective districts, or upon the high seas; where no other punishment than whipping, not exceeding thirty stripes, a fine not exceeding one hundred dollars, or a term of imprisonment not exceeding six months is to be inflicted....And shall also have cognizance, concurrent with the courts of the several States, or the circuit courts, as the case may be, of all causes where an ***alien*** *sues for a tort* ***only in violation of the law of nations*** *or a treaty of the United States* (Emphasis added).

Thus the alien tort claims act was born and still stands after 212 years. It had some use in the suppression of the illegal slave trade but it has lain dormant for decades. The requirements are a tort claim involving international law and the defendant having touched the Unites States at some time.

A succession of recent suits has breathed life back into this venerable act. Generally attempts to use this act to redress alleged political malfeasance in foreign countries have been dismissed on *forum non conveniens* grounds. The courts have been reluctant to enter even the foreign political arena. This has been left to international courts and tribunals as in Nuremberg, Uganda, Iran and Kosovo. The courts have not proven so reluctant where human rights outside of the political arena, particularly torture, have been an issue.

The pivotal, landmark success using the Alien Tort Claims Act was *Trajano vs Marcos*. Here several suits by Philippine citizens against the US resident former Philippine President Ferdinand Marcos resulted in a US$2 billion verdict and eventual settlement by the Marcos family for US$150 millions. Torture was the issue. Indictments have been filed trial is underway against Yugoslav Ex-President Slobodon Milosevic. More important for our consideration is extension of human rights from torture to environmental contamination. A group of Ecuadorian citizens have filed suit against Texaco under the Alien Tort Claim Act for environmental degradation as a consequence of drilling operations in Ecuador. This suit was dismissed by the circuit court on the grounds of *forum non conveniens* however the US Court of Appeals for the 2nd circuit reversed and remanded this case which is still pending. There is no Alien Tort Claims Act case yet that claims violation of human rights by defective consent for human research but this was a Nuremberg issue. In the US the Alien Tort Claim Act may trump *forum non conveniens* defense leaving a valid cause of action.

To join these observations an alien tort claim against a US citizen, resident or institution involving failure of consent in a research context could readily be brought in a US District Court with little fear of dismissal and arguable chance of success. Careful structuring of the research can provide a substantial measure of security and opportunities for defense.

Much benefit can be gained from careful study design. Where the study involves the testing of a drug or procedure and a successful drug or procedure is already in existence then it is probably prudent to avoid the use of a placebo. Test the new drug or procedure against the old drug or procedure. This avoids the issue of denial of care.

A formal contract with local physicians to provide the treatment will avoid claims of practice without a license.

Obtain liability insurance.

While careful study design, the use of independent contractors and insurance can help, the primary focus must be on issues of consent. The customs and behavior of the research subject must be respected. This may require obtaining the consent of an authoritarian figure in the community, or in the family, a form of substituted consent, group consent, governmental consent or a combination of the above to remain valid consent in the study country. It should also include the consent of the individual if it is to meet challenge in this country. Issues of consent by illiterate, uneducated, scientifically naive, medically naive individuals can only be addressed by vernacular presentation which is culturally sensitive and documented. Absence of coercion may be the most difficult issue to address and document. Rigorous adherence to protocol will help.

Knowledgeable legal review during preparation for the study is essential and should be a budgeted item in the grant to supplement ethical review. The two are separate and should remain so.

In summary, be careful with study design. Liability risk management includes insurance, and contractual limitation of liability. It is doubtful that customary malpractice insurance for physicians would apply. Individuals acting within the scope of their employment would share liability with the employer through vicarious liability. When the clinical research is contracted with a local physician or health department, it is possible to deflect liability by incorporating a hold harmless clause. Contract language may deflect a claim of practicing medicine without a license as well.

The strongest defense is associated with developing and using a cultural and literacy sensitive consent procedure. The consent may incorporate individuals other than the subject but no one substitutes for the individual patient's consent. Consent should be confirmed by signature or fingerprint. Published reports should refer to informed consent. Cultural constraints with regard to confidentiality and disclosure may preclude research in some countries.

Nothing but withdrawal from a proposed study can absolutely protect investigators from liability in international clinical research. Careful planning and documentation of the consent process coupled with other defenses can markedly reduce the likelihood of litigation.

To make these legal risk management tools meaningful they must be implemented within a research context that is ethically and morally defensible. This issue has been elegantly discussed in a paper by Costello and Zumla (2,000) in the British Medical Journal last year. They advocate applying a check list prepared by the Swiss Commission for Research Partnership with Developing Countries in the planning of research in these locations. This checklist addresses four main topics:

☛ Mutual trust and decision making
- Do partners know each other well and trust each other?
- Do partners have regular and easy communication?
- Do partners have good access to the databases and information from international organizations?
- Who proposed the research program?
- Do all participants understand it?
- Did people who will be affected by the research participate in developing the research theme?
- Were users consulted?
- Are the likely beneficiaries of the research clearly defined?

☛ National ownership (ensuring that research programs are owned and managed by nationals, with foreign inputs simply technical and advisory)
- Do national partners have overall administrative responsibility and responsibility for scientific supervision? If not, why not?
- Is there transparency, with equal access of partners to scientific and bugetary documents and fund allocation decisions?
- Do national partners have adequate training and audit systems to take full responsibility for program implementation?
- Are there clear and fair rules about who has authority over financial decisions?
- Will the partners share equally in any findings or potential commercial value, and has an agreement been made?

☛ Early planning for translation of research findings into policy and practice
- Does the research give due consideration to the social, political, economic, and technical situation of the partners?
- Is traditional knowledge and custom incorporated into the research plan?
- Is there a dissemination plan? Does this include publications and reports for the people directly affected by the research and by a wider audience than the scientific community?
- What is the plan about targeting government and non-governmental policy makers, stakeholders, and opinion leaders?
- Is authorship of scientific publications balanced?
- What steps are being taken to ensure that research findings will quickly be put into practice?

☛ Development of national research capacity
- Does the research fit into existing national or regional research policy?
- Is the collaboration being monitored and evaluated both internally and externally?
- Are national partners properly represented in evaluations?
- How will partnership develop local research capacity in the field of interest?
- Who will receive training, where and for how long?
- How will South to South collaboration be promoted?
- What will happen to staff when existing research projects finish?
- Will this research partnership reduce the migration of researchers to the developed world or into the bureaucracies of international agencies?
- How will the partner institution sustain research and continue research after the program is finished?

Taken together the checklist and risk management will permit investigators to pursue research objectives in a fashion which is ethically, morally and legally safe and sound.

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