Ethical Review and the Globalization of Clinical Trials
Defining Policy through Action

On October 2nd the Inspector General of the US Department of Health and Human Services (DHHS), Janet Rehnquist, released a report entitled *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects*.[i] This report marks a significant point in US policy toward the protection of human subjects in foreign clinical trials. It provides a needed impetus, along with clear direction, for a full US framework that will ensure the highest level of protection for clinical trial participants abroad. Just as importantly, the report marks an historical benchmark in biomedical research. Ten years ago it would have been awkward to speak of 'the globalization of clinical trials', let alone title a pivotal report with such an ominous (and promising) burden. During the 1990's industry-sponsored research moved rapidly beyond the familiar territory of the United States, the European Union, and Japan (the so-called ICH regions) into large parts of Central & Eastern Europe, South America, Asia, and Africa.[ii]

While the primary purpose of this Report is to assess the capacity of the Food and Drug Administration (FDA) for human subject protections in foreign clinical trials whose data is to be submitted for FDA approval – thus, nearly entirely industry-sponsored research – the Report also provides an overview of current oversight available in the United States regarding protections for research participants on foreign soil. Its recommendations are directed, not only to the FDA, but also towards "integrated approaches that would apply across Federal agencies and to federally funded and New Drug Application research conducted at non-U.S. sites." Specifically, it cites – and encourages the expansion of – the leadership role of the DHHS Office for Human Research Protections (OHRP).

A major finding in the Report is that there is generally a lack of knowledge with regard to the performance of foreign Institutional Review Boards (IRBs) (or, more generically, ethics committees). Not only does the FDA (and other Federal oversight agencies) have an incomplete understanding of the operation and quality of ethical review in clinical trials outside the United States, there seem to be well-founded reasons for concern with regard to the independence and quality of IRBs in many foreign institutions. Thus, the Report rightly recommends that FDA increase the information it has on foreign IRBs, contribute to capacity building for foreign IRBs (together with OHRP, the National Institutes of Health, and others), and that OHRP encourage a voluntary system of accreditation for foreign IRBs. The Report also points toward the responsibility of sponsors of foreign clinical trials, stating: "sponsors should take steps to educate the non-U.S. boards [IRBs] that they use".

The need to develop an integrated approach to information gathering, capacity-building, and voluntary accreditation of foreign IRBs across federal agencies and in cooperation with sponsors and researchers could be a daunting task. If one examines ethical review systems and IRB authority, composition, and practices in the European Union alone – 15 largely well developed research environments and pharmaceutical markets – the findings are striking. No two countries have the same review structure, the same requirements for ethical review jurisdiction, or the same procedures for submitting and evaluating applications to IRBs. While since April 2001 these countries now share a European law[iii] that requires certain harmonization in the area of ethical review, human subjects legislation in the different EU member

states is at various levels of development and inevitably reflects national practices and values in ethical review. Transpose this situation to the 191 member states of the World Health Organization – countries (and regions) with enormous political, social, and economic differences – and the requirements for achieving understanding and harmonized ethical review practices in the globalized clinical trials marketplace are, at the very least, complex.[iv]

Based on broad experience in promoting and carrying out research and training in countries with high disease burdens and weak healthcare infrastructures, the UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases (TDR) launched a number of initiatives aimed at strengthening capacity for sound ethical and scientific research. In the area of ethical review, TDR/WHO has worked in collaboration with a number of leading organizations, including the OHRP, FDA, European Forum for Good Clinical Practice (EFGCP), and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

A recent achievement of this partnership was the publication of the *Operational Guidelines for Ethics Committees That Review Biomedical Research*.[v] These Guidelines mark a significant contribution in the development of independence, competence, and quality in ethical review around the world. They provide a high standard of excellence encouraging IRBs and ethical review systems to grow and improve with a significant amount of autonomy. These globally accepted Guidelines establish guidance for IRBs concerning appropriate operating procedures. At the same time TDR/WHO and its collaborators recognized that guidelines are only a first, though necessary, step. Much more needs to be undertaken in capacity building for ethical review that will lead to sustained development at local, national, and regional levels.[vi]

International guidance and national legislation are essential to developing well functioning ethical review systems. However, international guidelines and national law alone will not suffice. Without a systematic approach to information gathering and capacity building, standards alone will not achieve greater protections for research participants through independent and competent ethical review in all countries. Given the enormous complexity of cultural variations, national laws, and local medical and research practices, local knowledge and local engagement is essential to develop ethical review. In addition, the principles of bioethics and the need for sustained development demanded that responsibility be borne at the local level, 'as close to the patient as possible'.[vii]

In a workshop held in Bangkok in January 2000, leading members of IRBs in Asian countries founded the Forum for Ethical Review Committees in Asia & the Western Pacific (FERCAP). In October 2000 a workshop organized in Mexico brought together leading members of Latin American IRBs, who then founded the Foro Latino Americano de Comités de Ética en Investigacion en Salud [Latin American Forum of Ethics Committees in Health Research] (FLACEIS). This was followed in January 2001 with a workshop in Zambia where leading African members of IRBs founded the Pan-African Bioethics Initiative (PABIN), an initiative originally launched by the African Malaria Vaccine Testing Network (AMVTN). Then in March of 2001, the Pasteur Institute in St. Petersburg and the Russian Medical Association, together with the European Forum for Good Clinical Practice (EFGCP), held a workshop where

leading experts from across the Confederation of Independent States founded the Forum for Ethics Committees in the Confederation of Independent States (FECCIS).

These fora were constituted as independent, non-governmental organizations for the specific purpose of developing good ethical review practices at the regional, national, and local levels. They committed to the exchange of information and the development of national guidelines and local standard operating procedures, as well as the establishment of educational activities for members of IRBs. In the short history since their formation, each of these fora has become a key reference point for promoting legislative development and capacity building activities in the region.

After nearly two years of TDR preparation in developing regional and national capacity for ethical review, a new initiative extends the work of a global partnership. The activities leading up to the organization of Strategic Initiative in Developing Ethical Review (SIDCER) are based on an increasing international awareness of the need to develop capacity for biomedical research that addresses the needs of the populations and communities where the research is undertaken. The SIDCER project focuses on developing best practices in ethical review by strengthening regional and in-country capacity. This initiative reflects an increasing commitment on behalf of researchers, sponsors, and oversight agencies to assist in the development of ethical review according to the highest standards.

The Initiative is being developed as an international, independent cooperative project to address the needs (now stated in the Inspector General's Report) of exchanging information and developing capacity in ethical review collaboratively, through the regional fora, and across public and private sectors. Ethical review is an essential part of the research enterprise. Yet in nearly all countries IRBs are undervalued and under-resourced. Regulatory authorities, funders, sponsors, and researchers have a responsibility to ensure that their research is examined by independent and competent (and perhaps, eventually, accredited) IRBs in appropriate ethical review systems. Where this essential human subject protection is missing, or inadequate, there is a shared responsibility to develop the needed capacity. No one authority, no one agency, no one country should be burdened with the responsibility of creating best ethical review practices in a globalized clinical trial environment. It would not be feasible; it would not be ethical; and it simply would not work.

SIDCER is being developed as an international cooperative project following on initiatives taken by TDR/WHO in collaboration with other organizations around the world. It strengthens human subject protections by driving capacity-building activities through the WHO regions into in-country institutions and human resources. The resulting network of regional fora of IRBs are able to develop their own capacity-building activities according to international standards and in cooperation with one another as well as with the support and guidance of leading US and international agencies and international research organizations. Meeting the challenges of human subject protections in the globalized environment of biomedical research today requires a concerted, international commitment.

Of significant importance in the Inspector General's Report is the recognition of the shortcomings of current oversight systems for human subject protections. More significant is the Report's strong recommendation that federal agencies, sponsors, and researchers cooperate to achieve systems and engagements that improve oversight and practices regarding ethical review in foreign clinical trials. These systems and activities will necessarily have to be linked to sovereign and independent systems for ethical

review (some more, some less, advanced) now found in nearly all 191 WHO member countries. Similarly, other countries and international research organizations also need to have assurance that their (foreign) studies meet with sound ethical review and address the health needs of the communities where the research is undertaken. The globalization of research requires a global approach to developing ethical review.

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[i] Office of the Inspector General, Department of Health and Human Services. *The Globalization of Clinical Trials: A Growing Challenge in Protecting Human Subjects.* September 2001. OEI-01-00-00190. Accessed October 3, 2001(See http://www.hhs.gov/oig/oei/reports/a542.pdf).

[ii] For an overview of the recent globalization of clinical research, see the Millennium Issue titled 'Good Clinical Practice in a Global Research Setting: Achieving Best Practices in Ethics & Science', Crawley, FP, Guest Editor. *Good Clinical Practice Journal*.' 1999;6.6.

[iii] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official Journal* L121 34-44, 1 May 2001.

[iv] See Crawley, FP. 'Ethical Review Committees: Local, Institutional, and International Experiences.' La bioéthique: entre juges et comités. *Journal International de Bioéthique* 1999;10.5:25-33

[v] TDR World Health Organization. *Operational Guidelines for Ethics Committees That Review Biomedical Research*. Geneva: TDR WHO 2000. .Accessed October 3, 2001 (See http://www.who.int/tdr/publications/ethics).

[vi] Crawley FP, Himmich H. 'Capacity-building and the role of communities in international biomedical research', *Biomedical Research Ethics: Updating International Guidelines*. A Consultation. Geneva: CIOMS, 2000: 231-244.

[vii] Lansang, MA, Crawley, FP. "The Ethics of International Biomedical Research." Editorial. *BMJ* 2000;321:777-8.