

Building Infrastructure: Good Clinical Practice and Ethical Review

Risk to participants in clinical research and to assessing benefit and risk, based on limited data, is managed through a systematic approach. One of the fundamental steps to assure subject protection is an independent review of research protocols, before the study begins, by a committee or board of experts. International and local country standards guide the composition of the board, what must be reviewed and mechanisms for recommending changes to study designs and the informed consent disclosure and documentation that will be made to patients about the proposed study. This independent body of experts analyzes the proposed study, the benefits and risks of the study, cultural considerations relevant to the study, and can make suggestions for changing the study.

A key challenge for international research is the fact that not only laws, regulations and standards for trials vary between countries, but the expertise for reviewing a trial can be hard to find, especially in lower resource, developing countries. One could address this difficulty by looking exclusively at what the local requirements are for such review, or potentially by submitting a proposed trial to an ethics committee in a more developed market. Doing so raises different concerns as to whether just following local laws and regulations is sufficient, and whether obtaining an independent ethics committee review, outside the country, is in the public interest. Across cultures, there is clearly a benefit and interest in having such reviews done locally, as much as possible. Building research ethics committees are thus a key infrastructure for managing research international trials:

[While the ethical review process is] "...typically undertaken by independent Research Ethics Committees (RECs), there are still many countries in the developing world in which these bodies are absent, ineffective or under-resourced. In addition, there may not be a pool of sufficiently trained and independent people to serve on such committees. As we have said, the inequalities in resources that exist between developed and developing countries pose significant risks of exploitation when externally sponsored research is carried out. The structure of RECs, the scope of their work and the mode of their operations are therefore particularly important in the context of research in developing countries."¹

¹ The Nuffield Council on Bioethics, "The ethics of research related to healthcare in developing countries: a follow-up Discussion Paper based on the Workshop held in Cape Town, South Africa 12–14th February 2004," 2005, http://www.nuffieldbioethics.org/fileLibrary/pdf/HRRDC_Follow-up_Discussion_Paper001.pdf

Building Ethics Infrastructure: Practice

The following describe some key challenges Pfizer has faced in doing international trials and in addressing local issues.

India

Pfizer was one of the first pharmaceutical companies to conduct malaria trials in India. In the mid-1990's, Pfizer approached a very large hospital and academic medical center in India to determine its interest in collaborating on a research study. The Pfizer research director responsible for the trial was delighted to be working with her alma mater and met with the relevant deans and department heads to discuss the project. Once the decision was made to pursue the effort, site visits were conducted and everything seemed in order to begin recruiting patients for the trial.

Just before the trial was to begin a change was made to the study protocol which necessitated a new approval by the institutional review board. To the amazement of the Pfizer research director, the hospital received a positive response from the IRB just an hour after the request had been submitted!

What Pfizer found in India was not exceptional-- In this instance, the head of the IRB was also the chairman of the relevant medical school department conducting the study. Furthermore, the rest of the IRB consisted of other department chairmen from the school. However, across cultures and research ethics standards, independence is integral to a review by an ethics committee.

Pfizer postponed the study and asked for the IRB to be reconstituted with members who were not involved in the proposed research protocol. The incident triggered the development of independent IRBs and working with Pfizer's quality assurance group, other Indian medical facilities established more independent review committees.

Suriname

Suriname is a small country of just under half a million people located on the northern coast of South America. Most of the land area is tropical rain forest and almost half of the nation's population lives in the capital city of Paramimbo,.

As the "smallest independent country in South America,"² Suriname has worked closely with various international entities to conduct clinical research for several decades. The U.S. Naval Medical Research Center Detachment (NMRCD), for example, has research partners throughout the region, including in Guatemala,

² The World Factbook, Central Intelligence Agency.

<https://www.cia.gov/library/publications/the-world-factbook/geos/ns.html>

Nicaragua, Costa Rica, Belize, Honduras, Suriname, Venezuela, Colombia, Ecuador, Bolivia, Chile, Uruguay, Paraguay, and Argentina.

When Pfizer went to Suriname to investigate whether the local government and medical research institutes were interested in conducting clinical studies, the IRB of record was the U.S. Navy. Suriname was a country that did not have its own IRB.

While it was permissible for Pfizer and others to conduct studies under the ethical review of the local, U.S. Navy chartered, IRB, it seemed important to the Pfizer team go a step further and help establish an independent ethics review board. Building on its experiences related to building ethical infrastructure in India, Pfizer approached the Ministry of Health in Suriname about the concept of creating an independent review committee.

Pfizer put resources and expertise on the table to assist the Ministry in recruiting qualified experts, setting up operational rules such as how often the board should meet, and in providing training on what to look for in research protocols and informed consent documents. Perhaps most importantly, the Ministry was encouraged to create a permissive environment for reporting negative information such as weak informed consent documents or possible adverse events. After a series of discussions, the Ministry set up an Ethics Council in 2005.

Building Ethics Infrastructure: Programs

In addition to running trials, Pfizer has a long-standing commitment to supporting training on good clinical practice (GCP). GCP is critical to international trials because it shows ethical and quality standards are being followed assuring the public that subject's rights are being protected and regulators that the study data is credible. The company's support has included lectureships at universities, active participation in international organizations and support of specific programs. Below are some recent examples.



European Forum for Good Clinical Practice (GCP)

Pfizer was the first corporate member of the European Forum for Good Clinical Practice, an influential GCP organization building awareness of GCP within and outside of Europe. The Forum's purpose "is to promote Good Clinical Practice (GCP) and encourage the practice of common, high-quality standards in all stages of biomedical research throughout Europe and globally. The EFGCP does this by promoting contact and partnership between the major disciplines and organisations affected by good clinical practice: pharmaceutical companies; contract research organisations; suppliers of services, systems and equipment; academia; investigators; ethics committees; regulatory authorities; patient organisations."³ While the organization is based in Europe, like Pfizer, it seeks to help develop the knowledge of GCP throughout the world.



World Federation for Medical Education

The World Health Organization (WHO) and the World Federation for Medical Education (WFME) have issued global standards for medical pre-and post-graduate education. Local accreditation and quality assurance capabilities assist in building quality health education. As of May 2007, the WFME Trilogy Global Standards are used in self-evaluation, peer review and other reform processes in more than 250 medical schools world wide, and used as a template for national/regional standards and for recognition/accreditation procedures in more than 60 countries.

Pfizer is assisting in a program to help establish self-evaluation capacity and accreditation systems in at least six countries, two in the Middle East, two in South East Asia and two in Latin America.

Based on needs assessment, the program seeks to provide specific support necessary for building self-evaluation capacity and accreditation systems in medical schools in developing countries. Pfizer participates by sharing its experience with quality assurance, reporting standards when using vendors and conducting site audits in order to build the knowledge necessary for medical schools in developing countries to meet the WFME Trilogy Global Standards and ultimately become accredited.

³ European Forum for Good Clinical Practice.

<http://www.efgcp.be/html.asp?what=AboutEFGCP.htm&L1=2&L2=0>



Lectureship at Steve Biko Centre of Bioethics

To increase the awareness and understanding of medical ethics in Sub-Saharan countries, Pfizer sponsors a four-year lectureship at the Steve Biko Centre for Bioethics, part of the University of Witwatersrand, in Johannesburg. Pfizer hopes the relationship with the Centre will ultimately provide a better basis for doing clinical trials in Sub-Saharan countries by improving the knowledge and application of ethical principles of clinical research. Courses in the lectureship include:

- Clinical Bioethics
- HIV: Bioethics & Health Law
- Research Bioethics

The Research Bioethics course examines topics such as “what constitutes unethical research, relevant national and international regulations and guidelines for research ethics, protocol reviews, case studies and standards of care in a study, authorship guidelines and plagiarism...Specific topics included are obtaining valid informed consent considering specific subgroups, standards of care for trial participants, access to study medications following completion of a clinical trial, issues pertaining to incentives affecting researchers and participants, releasing and publishing research results and the implementation of research findings.”⁴



Association of Good Clinical Practice in Nigeria (AGCPN)

The Association of Good Clinical Practice in Nigeria (AGCPN) offered three training programs funded and attended by Pfizer. The programs trained 82 local physicians and health scientists in ethics and principles of clinical research leading to accreditation for conducting clinical trials. The AGCPN was founded in 2006 and has over 200 members, including physicians, nurses, pharmacists, and biomedical scientists. Its long-term goal is to build up the infrastructure for biomedical research in Nigeria by increasing the number of physicians and institutions capable of conducting clinical research. Pfizer support and involvement and provides practical experience, as well as improved access to researchers by Pfizer medical staff. The Pfizer-sponsored courses were 3 day “train-the-trainers” workshops, which took place in September, 2008, in the university cities of Ile-Ife, Zaria, and Enugu. Workshop faculty included a Pfizer physician-scientist, as well as clinicians from medical schools, and researchers from clinical research organizations.

⁴ Bogaert, D. “Information Handbook: *Update MSc Med (Bioethics & Health Law)*,” Steve Biko Centre for Bioethics, Faculty of Health Sciences, School of Clinical Medicine, University of the Witwatersrand, Johannesburg South Africa
<http://web.wits.ac.za/Academic/Health/Entities/Bioethics/Courses.htm>

Discussion Questions

1. Who is responsible for creating ethical review committees?
2. What role, if any, should private pharmaceutical companies play in helping create, train, or support such committees? Are the public health interest and the pharmaceutical company's interest likely to be aligned or divergent?
3. How should local experts be trained in ethical decision making as related to the practice of medicine? The conduct of clinical trials?
4. What role, if any, should private pharmaceutical companies play in educate or train local experts? Are the public health interest and the pharmaceutical company's interest likely to be aligned or divergent?
5. What long-term effects might strengthening ethical expertise in foreign countries have?
6. Should pharmaceutical manufacturers partner with regulators in training and other types of collaboration to build ethical infrastructures? Why or why not?