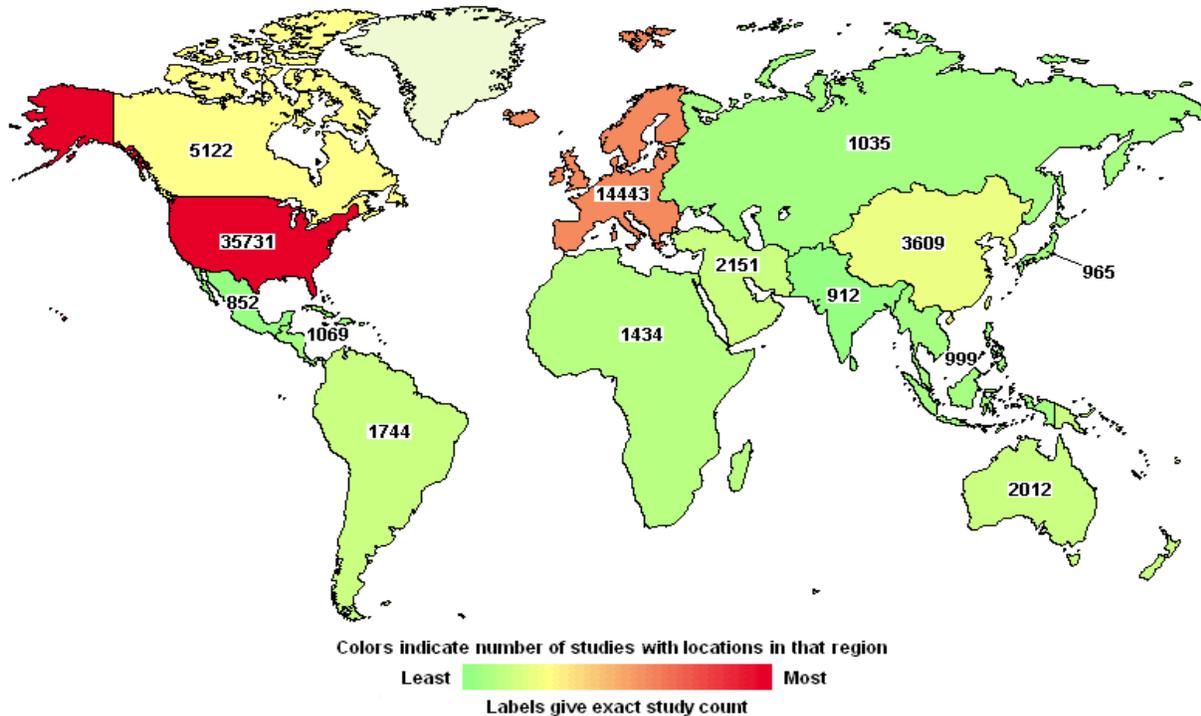


AAHRPP: Assuring Ethical Standards in Human Research

As of June 2008, there were more than 63,000 clinical studies being conducted worldwide. The United States accounted for 35,731 and Europe 14,443.¹

Map of All Studies in ClinicalTrials.gov



It seems a basic assumption clinical research would be conducted ethically. But how do we know if research is being conducted at the highest standards of excellence? Are certain researchers or research centers certified or recognized for their programs? Quality is often difficult to assess and measure but a critical component for a business predicated on maintaining trust with patients, physicians, and regulators.

Accreditation as a means for improving human subject protection

The Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) was started in 2001 with the idea of using an accreditation process to ensure “**excellent, ethically sound research**” is conducted at research sites in the U.S. and internationally. AAHRPP had two primary goals: 1) strengthening human research protections and 2) improving the quality of research. As of the summer of 2008, 129 institutions had received accreditation from AAHRPP representing more than 550 entities and including:

- 42% of the nation’s research-intensive universities

¹ <http://clinicaltrials.gov/ct2/search/map> Downloaded October 21, 2008.

- 36% of U.S. medical schools
- 52% of Department of Veterans Affairs facilities²

Value of Accreditation

Human clinical research is conducted by a number of different types of organizations. Two recently accredited entities provide insights into why accreditation is sought.

In March of 2008 two "first of its kind" organizations were accredited -- Florida's Department of Health and Pacific Northwest National Laboratory (PNNL), representing the first state health department and the first U.S. Department of Energy (DOE) research laboratory to the accredited members of AAHRPP. Both organizations pursued accreditation, in part, as a way to showcase to the public their high standards of research protection.

"For PNNL, accreditation is 'a visible way of demonstrating that we value research protections for human subjects and that we are worthy of our clients' confidence and collaboration in research,' says Sherry Davis, Manager of PNNL's Human Research Protection Program and IRB. 'It was important to our laboratory to take our place among institutions that have earned this prestigious distinction.'"³

The state of Florida Department of Health also noted two other benefits: competitiveness when competing for grant funding and an improved ability to build the infrastructure necessary to conduct excellent research. The accreditation for the Florida government included 67 county health departments.

"State Surgeon General Ana M. Viamonte Ros, M.D., M.P.H., called on 'all research institutions in Florida to join the department by pursuing best practices, ensuring ethical conduct of research, and protecting participants in research.' She cited a number of benefits of accreditation, including a competitive edge when seeking agency funding and an improved infrastructure for research."⁴

More than 400 entities are currently seeking accreditation from AAHRPP. The current voluntary accreditation model, however, is relatively new and is the result of a difficult passage in the development of today's clinical research environment.



² "22 Join Accredited Organizations; AAHRPP on Track to Meet Goals," *AAHRPP Advance*, Summer 2008, p. 7.

³ "More than 100 Organizations Now Accredited," *AAHRPP Advance*, Spring 2008, p.3.

⁴ Ibid.

Assuring Participant Protection: Who is Responsible?

Federal regulations are clear in assigning responsibility for protecting human subjects to institutional review boards (IRBs).⁵ Every clinical research study involving human subjects must be reviewed and approved by an IRB before the study can be commenced. IRBs are made up of at least five people, some scientific experts and some laypersons, who are asked to determine whether the proposed research project will treat people ethically during the study and is worth completing because the benefits of what will be discovered during the study outweigh the risks. IRBs are also responsible for making sure potential participants are given all the information they need to decide whether to participate in the study through the informed consent process.

In addition to IRBs, layers of oversight are in place to assure participants are protected during human research. University research centers have oversight boards, for example, and several regulatory bodies at the state and federal level have jurisdiction in enforcing compliance at research centers. In the late 1990's, however, some prominent cases of research misconduct at Veterans Affairs (VA) facilities and academic medical centers alarmed regulators. The Department of Health and Human Services' former Office for Protection from Research Risk (OPRR)⁶, suspended research programs at a VA facility in Los Angeles, Rush-Presbyterian Medical Center in Chicago, and Duke University Medical Center in North Carolina.⁷ The protection of human research subjects was of major concern to the American public at this time:

"There is a sense of crisis in the country about the effectiveness of the nationwide system that protects the rights and welfare of human research subjects. Reports of problems appear on television or in newspapers almost weekly and focus attention on the system's centerpiece, the institutional review board (IRB). University hospitals' entire research programs have been suspended on grounds of inadequate IRB performance, and governmental agencies have found that the IRB system is incapable of coping with its workload."⁸

In response to the crisis, the VA awarded a multi-million grant to the National Committee for Quality Assurance to create an accreditation program for its medical facilities. Shortly after, academic medical centers (medical colleges with affiliated hospitals or health systems), joined forces to fashion a solution to

⁵ See CFR 45, Part 46 "Protection of Human Subjects" <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.103>

⁶ Now the Office of Human Research Protections (OHRP).

⁷ Science, 2 April 1998, p. 18, 6 November 1998, p. 1035, and 19 May 1999, p. 1246.

⁸ Levine, R. "Institutional Review Boards: A Crisis in Confidence," *Ann Int Med* (2001) 134:2, p. 161.

restore confidence in the U.S. medical research enterprise by creating AAHRPP to grant accreditations of non-VA facilities.

The free market allowed the two competing entities to work to accredit the approximately 3,000 to 5,000 research organizations in the U.S. but by the end of 2005, AAHRPP became the sole provider of the accreditation "gold seal" exemplifying the highest standards of human participation protection. The focus has now changed from an oversight approach whereby the IRB is seen as primarily responsible for participant protection to an institutional approach that "motivates everyone involved to be part of what now increasingly is called 'a culture of conscience and compliance.'"⁹

Accreditation Process

Instead of looking backward and using quantitative standards to assess an organization's human research protection program, the current human protection accreditation system looks forward to what organizations say they will do to protect subjects and examines best practices. AAHRPP's website states the following:

"Strive for protection, not perfection. The goal is to have an effective Human Research Protection Program, whose activities achieve the desired outcome: to protect research participants. If practices and policies meet the AAHRPP Element and Standard, do not spend time revising them further. Instead, focus your energy on identifying and correcting gaps."

There is a three step process:

1. Self-assessment and application preparation
2. On-site evaluation
3. Council review

The process begins with a self-assessment and each applicant organization is asked to analyze its own standard operating procedures against 22 standards and 77 elements in all. The assessment is meant to identify gaps and areas for improvement. After the self-assessment is complete, the organization submits an application form along with a 10-page overview of the organization's human research protection program and copies of all the documentation to support the program.

Once the application package is reviewed and all gaps and areas of improvement identified by AAHRPP have been addressed, an on-site evaluation is conducted. Within 30 days, a draft site report is generated and sent back to

⁹ Mather, J and Harnett, T. "HSP and Accreditation: Growing Pains and Successes Mark First Seven Years," *Medical Research Law & Policy*, (2008) Vol. 7, No. 4.

the applying entity. The research organization then has 30 days to respond in writing with any corrective actions the entity has taken. The response, site visit evaluation and original application are then considered by the Council and a final decision regarding accreditation is communicated to the applicant.

The process, by design, requires organizations to demonstrate extensive safeguards are in place at every level of their research operation. "AAHRPP's standards exceed federal regulations by requiring organizations to address conflicts of interest, to provide community outreach and education and to apply the same stringent protections to all research involving human participants."¹⁰

Reasons not to Seek Accreditation...

The concept of accreditation is not without costs and risks, however. First of all, getting Pfizer's documentation collected and organized for review by AAHRPP is a huge project. Putting together the application for Pfizer ended up requiring the assistance of 12 people for an effort that lasted for seven months. This supporting documentation for Pfizer's application was 1,234 pages long.

Additionally, AAHRPP may and will change its requirements over time. Maintaining accreditation is likely to become more difficult, as additional standards are adopted, and letting accreditation lapse is likely to be embarrassing and awkward to explain.

Accreditation of an organization's phase 1 research program may also raise questions as to why the phase 2, 3, and 4 research is being done at academic medical centers and research sites that don't have accreditation. It's possible that such research could be criticized as being done with less rigor or oversight, in not having an accreditation of all of the local institutions doing that research for the sponsor.

Addressing the last concern first, most of Pfizer's research is done at institutions where key researchers or patient groups are located and therefore, the Company's ability to choose an IRB or ethics committee is constrained by the fact that these institutions use a specific IRB or ethics committees, affiliated with the institution, which may or may not have accreditation. Outside the U.S., it is especially difficult to even find accredited ethics committees at present. Pfizer tried to raise the bar, within the U.S. by deciding to use only accredited central IRBs for its phase 2, 3, and 4 trials. Outside the U.S., the Company is looking at ways to support and encourage accreditation and other quality standards for research. There will always be some variability in local standards of course. So,

¹⁰ AAHRPP News Release, September 18, 2008. <http://www.aahrpp.org/www.aspx?PageID=248>

for Pfizer, starting down this path by seeking accreditation of its global phase I program, using accredited central IRBs in the U.S., and encouraging voluntary accreditation of research sites (in the U.S. and outside the U.S.) is an important catalyst for additional capacity and consensus building. As other research sponsors undertake similar efforts, the prospect for voluntary accreditation is likely to gain steam internationally and improve the quality at local research sites wherever in the world they are located. It is also true that most research sites are already operating under international Good Clinical Practice (GCP) Standards, so accreditation will supplement oversight by research sponsors and regulators, of the implementation of GCP at sites in different countries and within different cultures.

Pfizer Seeks Accreditation for its Phase I Units

Ordinarily, sponsors are not eligible for accreditation since they do not “conduct” research. Pfizer, however, owns and operates three clinical research centers (PCRUs), which conduct phase I trials in :

- New Haven, Connecticut
- Brussels, Belgium
- Singapore City, Singapore

The PCRUs are specifically designed to execute clinical studies in a Pfizer-owned setting that provides both comprehensive clinical care and state of the art medical technology. The PCRUs are bound by all Pfizer corporate policies and procedures, as well as those of PGRD in the conduct of human research and the protection of human subjects.

If successful in its application for accreditation by AAHRPP, Pfizer will likely be the first pharmaceutical company to obtain that mark of excellence, which recognizes human research programs demonstrating the highest ethical and regulatory standards. The president of a large, accredited IRB in the U.S. said Pfizer’s pursuit of AAHRPP accreditation “demonstrates [the company’s] commitment to and leadership in human research protections.” He went on to say, “It would be good to see all the sponsors adopt this level of commitment.”

Pfizer, in recognition of the imprimatur of quality accreditation brings, also took the additional step of requiring accreditation of IRBs in the U.S. that do centralized reviews of research sponsored by Pfizer. On November 18, 2008, Pfizer decided to stop using centralized institutional review boards in the U.S. that did not have or were not pursuing accreditation with AAHRPP. This was done in recognition of the fact that there are enough accredited, high quality IRBs with accreditation in the U.S. to make that a requirement for selection of central IRBs by Pfizer study teams. The decision also recognizes that accreditation is a good metric, albeit not the only one, of a quality system for reviewing research.

Publication note:

On April 3, 2009, following a 15-month examination of the Company's program for its U.S., Belgium, and Singapore clinical research units, Pfizer become the first pharmaceutical company to be accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

Discussion Questions

1. Should an entity sponsoring clinical research also be permitted to achieve accreditation for research centers it owns? Why or why not?
2. As a potential patient in a research study, would you consider the site's accreditation status as important to your decision whether to participate in the clinical trial?
3. Is the current accreditation model of clinical research centers likely to provide more extensive protection for human subjects than the previous system that relied on more heavily on institutional review boards?
4. What role should the following types of organization play in protecting human subjects in clinical research?
 - Government
 - Private industry
 - a. Sponsors
 - b. CROs
 - c. Clinical research sites
 - Non-governmental organizations