

## Expanding Human Research Oversight

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Overwhelmed by all the changes and proposed changes in the system to ensure human subject protection? It is an important subject and one in which everyone is interested. Being *for* human subject protection is like being *for* Mom. However, we all know that *Mom* sometimes can be a handful! So I shall quickly review how we got to where we are, what is being done, and who is doing it. The table at the end of this article provides an additional summary of the current state of human subject protections.

### HOW WE GOT HERE

The current system of human subject protection was built 30 years ago with Institutional Review Boards (IRBs) as the cornerstone. Some well-publicized system failures in the last decade prompted evaluations that identified increasing volume and research complexity as primary threats to the system's effectiveness. In response, the Department of Health and Human Services (DHHS) Office of Inspector General (OIG 1998), and the National Bioethics Advisory Commission (NBAC 2001) issued recommendations calling for education and reform. Since then, initiatives in pursuit of these objectives have been rolling out non-stop.

### WHAT IS BEING DONE

The Office of Human Research Protections (OHRP) is leading the effort for DHHS, holding noncompliant research organizations accountable, while expanding the government's capacity for oversight, monitoring, and educating the research community. OHRP already has leveraged resources by: (1) implementing a unified federal registration system for all IRBs that identifies where IRBs are, how they are constituted, what kinds of research they are reviewing, and what volume of work they handle; (2) implementing a streamlined assurance process allowing all federal agencies to recognize a single, common assurance and avoid redundancy. The assurance is a commitment from any entity that receives federal funds for research to follow federal rules for protection of research subjects; and (3) redeploying resources from the process of negotiating assurances to support-

ing quality improvement, including increasing the number site visits and providing IRBs with tools for self assessment and guidance for improvement.

The goal is to prevent problems before they occur, and positive reinforcement and supportive training are the preferred themes. OHRP does wield a big stick and can shut down clinical studies in response to lax oversight, but it also has developed a big carrot by creating a national awards program to recognize excellence in protection of human research subjects—e.g., best practices, innovations in protecting research volunteers, and lifetime achievement for outstanding protection activities.

Dr. Greg Koski, Director of OHRP, also is working with other government agencies to consolidate and build a comprehensive program. OHRP has four goals for a new oversight framework: *Simplicity*, *Uniformity*, *Efficiency* and *Effectiveness*. Selecting representatives from throughout the federal government, Dr. Koski has created the “SUEE” task force to identify and eliminate inefficiencies between the various agencies’ human testing regulatory approaches. In addition, the SUEE task force will suggest improvements to current OHRP practices that can be achieved relatively quickly and easily.

OHRP is working in concert with the Food and Drug Administration (FDA), which in October 2001, established the Office of Good Clinical Practice (OGCP) to improve the conduct and oversight of clinical research and to promote the protection of participants in FDA-regulated clinical research.

#### CONGRESSIONAL DEVELOPMENTS

Although Dr. Koski is leading an aggressive charge to consolidate oversight across the federal government, many feel that reform will require legislation to succeed.

Action on Capitol Hill is encouraging Bush administration efforts to reform oversight of clinical research. The House International Relations Committee has approved a measure that protects individuals in clinical trials overseas. A six-part *Washington Post* series (17–22 December 2000), “The Body Hunters,” prompted an amendment to the Export Administration Act that, if finalized, will require drug companies to show that a U.S. ethics committee has approved the clinical trial as part of the application for authorization to export the investigational product.

Members of Congress also are considering legislation to expand federal oversight of human research studies and to impose penalties on noncompliant researchers.

- Representative Diana DeGette (D-CO) is leading efforts in the House to enact legislation to codify certain human research protections for both private and publicly funded studies.

- Senator Ted Kennedy (D-MA), chairman of the Senate Health, Education, Labor, and Pensions Committee, may offer legislation to establish a central federal clinical research agency, as recommended by NBAC.
- Legislation enabling the FDA and NIH to levy monetary penalties for violations of informed consent and other important research practices is also being pursued.

The Institute of Medicine's (IOM) assessment of the nation's system for overseeing human research, to be completed in the fall of 2002, may spur additional policy changes.

#### INSTITUTE OF MEDICINE

DHHS requested IOM to conduct a two-year study evaluating the structure of human subject protection activities, including but not restricted to IRBs. In April 2001, IOM produced recommendations for accreditation standards for research organizations. One of IOM's objectives is to identify ways to measure system effectiveness in order to establish models for improvement.

The IOM currently is examining the role and methods of *both* the private *and* public-sector organizations protecting human subjects. Previously, system examinations included only federal agencies, research institutions, and federally funded investigators. Since private sponsors and Contract Research Organizations also are responsible for subject protection and safety, they are well positioned to offer effective examples of successful practices.

#### ACCREDITATION

An early recommendation of NBAC that rapidly gained support is system accreditation, including Institutional Review Boards. The goal of accreditation is to develop performance standards that encourage "best practices" and to recognize programs that meet those standards. Accreditation complements the regulatory role of government and is applicable regardless of research type, location, or source of funding.

The Association for the Accreditation of Human Research Protection Programs (AAHRPP) was incorporated in April 2001, and Dr. Marjorie Speers, the former acting director of NBAC, was appointed as its executive director. AAHRPP's Accreditation Standards and Procedures, which reflect the findings of IOM, were released in October 2001 for public comment. These standards were refined during several AAHRPP pilot site visits, including one for intramural programs at the National Institutes of Health. As of February 2002, AAHRPP is accepting applications for accreditation from organizations that conduct or review research involving human participants. Both OHRP and FDA endorse this voluntary accreditation system.

THE WHITE HOUSE

A new presidential advisory group, the White House Council on Bioethics, chaired by University of Chicago bioethicist Leon Kass, has been created to consider the ramifications of biomedical innovation. President Bush announced the group as part of a program to permit limited government funding for stem cell research. It replaces the National Bioethics Advisory Commission whose charter expired in October 2001. The Council will monitor stem cell research and examine the ethical, scientific, and legal issues surrounding human cloning, assisted reproduction, genetic screening, gene therapy, euthanasia, brain implants, and psychoactive drugs.

OTHER KEY INITIATIVES

*IRB Registration*

OHRP and FDA have launched an online program to register all IRBs in order to facilitate oversight and enhance communication with IRB officials who are actively reviewing projects.

*Development of Central IRBs*

OHRP's Dr. Koski is promoting the "uncoupling" of IRB's from research institutions by having multiple institutions rely on accredited, centralized IRBs. A joint government/private-sector panel is developing good IRB practices to facilitate the effort, which will help to provide assurance that the central IRBs demonstrate expertise in overseeing complex research studies and assistance in defining cooperative responsibilities.

*Improved Monitoring*

OHRP and FDA are encouraging greater use of data and safety monitoring boards (DSMBs). NIH currently requires large-scale (Phase III) trials to have DSMBs and has issued guidelines supporting DSMB review for certain high-risk studies. The FDA recently issued additional guidance on the relationship between DSMBs and IRBs. The guidance specifies when DSMBs should be required, when they should be independent, their responsibilities, confidentiality issues, operational issues and qualified membership.

Separately, the Center for Biologics Evaluation and Research (CBER), which is responsible for regulating gene therapy research studies at the FDA, has formed a working group to evaluate the need for earlier agency review of sponsor monitoring plans.

### *Conflict of Interest*

To help IRBs evaluate programs, DHHS has issued a draft interim guidance on financial relationships involving investigators and institutions. Financial relationships between investigators, institutions, and research sponsors may influence the professional judgment and independence of those responsible for protection of human subjects. The guidance requires disclosure and evaluation of researchers' financial interests in a clinical program, including disclosure to potential participants, and addresses points of discussion when evaluating financial conflict.

### *Education and Training*

OHRP and FDA are working together to promote appropriate research bioethics training for clinical investigators, IRB members, and associated staff. Such training is currently a requirement of all clinical investigators receiving NIH funds and is a condition of the OHRP assurance process. The FDA is conducting educational programs for clinical investigators, jointly sponsored with industry and academic representatives. It also plans to revise the FDA Information Sheets that provide guidance for investigators and IRBs.

### *Informed Consent Policies*

One of the main goals of reform is to change the informed consent process from one that focuses on documenting consent to one that promotes subject understanding and voluntary participation throughout the course of the study. NIH and FDA are conducting studies on how well individuals currently understand research risks and benefits and methods to improve that understanding.

### *Adverse Event Reporting*

OHRP and FDA are working to reduce differences between their adverse event reporting requirements to make it easier for investigators to understand and comply with the rules.

## CONCLUSION

That is a lot of activity! Before all is done, there will be more acronyms and more reports, findings, advisories, recommendations, interim drafts, proposals, and probably lots of debate—all with one goal, human subject protection.

*Mom* would be proud!

REFERENCES

- NBAC. National Bioethics Advisory Commission. 2001. *Ethical and Policy Issues in Research Involving Human Participants*. 2 vols. Bethesda, MD: U.S. Government Printing Office.
- OIG. Office of Inspector General, DHHS. 1998. *Institutional Review Boards: A Time for Reform*. OEI-01-97-00193. Washington, DC: DHHS.

## HUMAN SUBJECT PROTECTIONS: WHO'S WHO, WHAT'S WHAT\*

| Who (When Established)   | Given authority by: | Purpose  | Current Work   |
|--|---------------------|--|--|
| <p><b>National Bioethics Advisory Commission (NBAC)</b></p> <p>(October 1995. Charter expired October 2001)</p> <p><a href="http://bioethics.gov/general.html">http://bioethics.gov/general.html</a></p> | President           | Advised on bioethics and public policy issues related to conducting human research. NBAC made recommendations to the White House and other departments and agencies. | <p><b><i>Final Report (August 2001):</i></b> Ethical and Policy Issues in Research Involving Human Participants<br/> <a href="http://bioethics.georgetown.edu/nbac/human/overvol1.html">http://bioethics.georgetown.edu/nbac/human/overvol1.html</a></p> <p>Addresses the adequacy of the current regulatory structure; and the institutional review board system.</p>   |
| <p><b>White House Council on Bioethics</b></p> <p>(November 2001)</p> <p>18 member panel</p> <p>First meeting: 17-18 January 2002</p>  | President           | Advise White House regarding ramifications of advances in biomedical science and technology.   | <p><b><i>Replacing NBAC</i></b></p> <p>Monitor embryo and stem cell research, and some other issues identified by NBAC as requiring serious and sustained discussion, i.e., assisted reproduction, cloning, uses of knowledge and techniques derived from human genetics or the neurosciences, and end-of-life issues.</p>   |
| <p><b>Department of Health and Human Services (DHHS)</b></p> <p>(May 1980 (formerly HEW))</p> <p><a href="http://www.hhs.gov/">www.hhs.gov/</a></p>  | President           | Protect the health of all Americans and provide essential human services   | <p><b><i>1. Setting the agenda for human subject protection initiatives.</i></b> Specific goals:</p> <ul style="list-style-type: none"> <li>• Expand education and training for all clinical investigators, IRB members and staff.</li> <li>• Enhance informed consent process and ensure more vigilant monitoring and oversight.</li> <li>• Ensure that researchers understand and comply with federal conflict of interest regulations.</li> <li>• Provide FDA with additional enforcement tools to enhance its oversight role.</li> </ul> |

\*Updated 1 May 2002 ©2002 Goodwyn Institutional Review Board, Ltd.

| Who (When Established)   | Given authority by:  | Purpose   | Current Work   |
|--|--|---|--|
| <p><b>National Human Research Protections Advisory Committee (NHRPAC)</b><br/>(Chartered June 2000)</p> <p>Director of OHRP serves as Executive Secretary.<br/><a href="http://ohrp.osophs.dhhs.gov/nhrpac/nhrpac.htm">http://ohrp.osophs.dhhs.gov/nhrpac/nhrpac.htm</a></p> | <p>Department of Health and Human Services (DHHS)</p>        | <p>Provide expert advice and recommendations to the Secretary of DHHS, Assistant Secretary of Health (ASH), the Director, Office for Human Research Protections (OHRP), and other departmental officials on a broad range of issues and topics pertaining to protection of human research subjects.</p> | <p><i>2. Issued regulations</i> (the Privacy Rule) to guarantee patients' rights and protections against the misuse or disclosure of their health records. <a href="http://aspe.bhs.gov/admsimp/final/PvcTxt01.htm">http://aspe.bhs.gov/admsimp/final/PvcTxt01.htm</a></p> <hr/> <p><b>1. Recommendations Issued</b> <a href="http://ohrp.osophs.dhhs.gov/nhrpac/doc-report.htm">http://ohrp.osophs.dhhs.gov/nhrpac/doc-report.htm</a>:</p> <ul style="list-style-type: none"> <li>• 45 CFR 46 Subpart D (Response to FDA decision re: waiving parental permission in certain research /certain children)</li> <li>• 45 CFR 46 Subpart B</li> <li>• Financial Relationships in Clinical Trial Research (Response to OHRP)</li> </ul> <p><b>2. Evaluating:</b></p> <ul style="list-style-type: none"> <li>• Human subject protections for non-biomedical research.</li> <li>• Declaration of Helsinki 2000</li> <li>• Human subject protections for research in children. (Response to Childrens' Health Act of 2000).</li> <li>• Genetic Studies, including family members / third parties and informed consent.</li> <li>• Privacy and Confidentiality, including implications of HIPPA and the Privacy Rule.</li> <li>• Informed consent and the decisionally Impaired.</li> </ul> |
| <p><b>Human Subjects Research Subcommittee (HSRS)</b><br/>Chaired by the Director, OHRP.</p>   | <p>Office of Science and Technology Policy (White House)</p> | <p>Develop integrated system of human subject protection across the <i>entire</i> Federal Government.</p>   | <p><i>Evaluating</i> specific international policies as well as big-picture initiatives to achieve <i>simplicity, uniformity, efficiency, and effectiveness</i> (the "SUEE" task force).</p>   |

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|--|---|--|--|
| <p><b>Office of Human Research Protections (OHRP)</b><br/>(June 2000)<br/><i><a href="http://ohrp.osophs.dhhs.gov/">http://ohrp.osophs.dhhs.gov/</a></i></p> | <p>Department of Health and Human Services (DHHS)</p> | <p>Oversee human research protections (federally funded)</p> | <p><b>Taking the lead in executing on human subject protection initiatives set by DHHS</b></p> <ul style="list-style-type: none"> <li>• Leveraging assurance filing program and registration of IRBs</li> <li>• Quality Improvement Program <i><a href="http://ohrp.osophs.dhhs.gov/humansubjects/qip/qip.htm">http://ohrp.osophs.dhhs.gov/humansubjects/qip/qip.htm</a></i></li> <li>• Providing guidance:</li> <li>• Financial disclosure issues for IRBs to facilitate unbiased discussion and properly informed research subjects (Draft) <i><a href="http://ohrp.osophs.dhhs.gov/nhrpac/mtg12-00/finguid.htm">http://ohrp.osophs.dhhs.gov/nhrpac/mtg12-00/finguid.htm</a></i></li> <li>• Research activities involving human embryonic stem cells (HESCs), HESC-derived test articles, human embryonic germ cells derived from fetal tissue (Issued 16 Nov 01) <i><a href="http://ohrp.osophs.dhhs.gov/references/HESCGuidance.pdf">http://ohrp.osophs.dhhs.gov/references/HESCGuidance.pdf</a></i></li> <li>• Written Institutional Review Board (IRB) procedures (Issued 02 Apr 02) <i><a href="http://ohrp.osophs.dhhs.gov/humansubjects/guidance/wir_bproc.pdf">http://ohrp.osophs.dhhs.gov/humansubjects/guidance/wir_bproc.pdf</a></i></li> <li>• Amended Subpart B of 45 CFR 46 to provide additional protections for pregnant women and human fetuses ; clarified provisions for paternal consent; clarifies language. (13 Dec 01) <i><a href="http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45_cfr46.htm">http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45_cfr46.htm</a></i></li> <li>• Sponsoring national awards program for excellence in human research protection. (15 Nov 01) <i><a href="http://ohrp.osophs.dhhs.gov/references/AEHRPPR.pdf">http://ohrp.osophs.dhhs.gov/references/AEHRPPR.pdf</a></i> <i><a href="http://ohrp.osophs.dhhs.gov/references/AEHRPJN.pdf">http://ohrp.osophs.dhhs.gov/references/AEHRPJN.pdf</a></i></li> </ul> |

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|---|---|---|--|
| <p><b>Food and Drug Administration (FDA)</b><br/>(1927)<br/><a href="http://www.fda.gov/">www.fda.gov/</a></p> <p>OGCP<br/><a href="http://www.fda.gov/oc/gcp/">www.fda.gov/oc/gcp/</a></p>   | <p>Department of Health and Human Services (DHHS)</p> | <p>Oversee marketed products and those intended for marketing.</p>  | <p><b><i>Providing guidance</i></b></p> <ul style="list-style-type: none"> <li>• Establishment and operation of Data Monitoring Committees. (Draft, 20 Nov 01). Comments due by 19 February 2002 <a href="http://www.fda.gov/ohrms/dockets/98fr/010489gd.pdf">http://www.fda.gov/ohrms/dockets/98fr/010489gd.pdf</a></li> <li>• OGCP established (June 2001) to focus on conduct and oversight of clinical research and to ensure the protection of participants in FDA-regulated clinical research/represents US in the International Conference on Harmonization of Requirements for Marketing...(ICH). <a href="http://www.fda.gov/cder/guidance/959fnl.pdf">www.fda.gov/cder/guidance/959fnl.pdf</a> (GCPs), <a href="http://www.fda.gov/cder/guidance/4155fnl.pdf">www.fda.gov/cder/guidance/4155fnl.pdf</a> (Choice of Control Group)</li> </ul> |
| <p><b>Institute of Medicine (IOM)</b><br/>Committee on Assessing the System for Protecting Human Research Subjects</p> <p>(Executing described function at the request of DHHS. A two year study.)</p> <p><a href="http://www.iom.edu/IOM/IOMHome.nsf/Pages/human+research+protections">http://www.iom.edu/IOM/IOMHome.nsf/Pages/human+research+protections</a></p> | <p>Department of Health and Human Services (DHHS)</p> | <p>Three-part study of the human research protection process.</p> <p>Develop accreditation standards for Institutional Review Boards (IRBs).</p> <p>Assess effectiveness of OHRP's activities.</p> <p>Identify a set of objective measurement techniques for the effectiveness of the human research process.</p> | <p><b><i>Setting the agenda for accreditation effort.</i></b></p> <p>IOM Report: Preserving Public Trust: Accreditation and Human Research Participant Protection Programs (April 2001) <a href="http://books.nap.edu/html/public_trust/summary.pdf">http://books.nap.edu/html/public_trust/summary.pdf</a></p>  |

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|---|----------------------------|--|---|
| <p><b>Public Responsibility in Medicine and Research (PRIM&amp;R)</b><br/><i>http://www.primr.org/</i></p>                                | Professional Association   | National organization - multidisciplinary forum for addressing biomedical and bioethical issues.   | <i>Draft standards</i> for accreditation of IRBs<br>IRB 101 Course (w/OHRP)   |
| <p><b>Applied Research Ethics National Association (ARENA)</b><br/><i>http://www.primr.org/</i></p>                                       | Professional Association   | Partner to PRIM&R – application of ethical principles, governmental regulations, and other policies involved with research and clinical practice | <i>Program for certification</i> of IRB administrators and members. (Council for Certification of IRB Professionals (CCIP))   |
| <p><b>Association for the Accreditation of Human Research Protection Programs (AAHRPP)</b><br/>(April 2001)<br/><i>www.aahrpp.org</i></p> | Created by 7 organizations | Offer accreditation to institutions engaged in research involving human participants using a voluntary, peer-driven, educational model.          | <p><i>Accreditation standards</i> released October 2001. The overall goal of accreditation is to improve protection of human research subjects by developing performance standards that encourage programs to adopt “best practices” in this area, and by recognizing the programs that meet those standards.<br/><i>http://www.aahrpp.org/interimprocedures.pdf</i></p> <p>The national program of accreditation will consist of two assessments: a self-assessment by the program itself and a peer review site visit. In order to accomplish these two steps, AAHRPP will undergo a four-step development process.</p> |