Testimony
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Committee on Energy and Commerce
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The Role of the HHS Office for Human Research Protections in Protecting Human Research Subjects

Statement of

Jerry A. Menikoff, M.D., J.D.

Director
Office for Human Research Protections
Office of Public Health and Science
U.S. Department of Health and Human Services

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Good morning, Mr. Chairman and members of the Subcommittee. I am Jerry Menikoff, Director of the Office for Human Research Protections (OHRP) within the Office of Public Health and Science, Department of Health and Human Services (HHS). I previously served as the director of the office that oversees the human research protection program at the National Institutes of Health (NIH), and as a bioethicist in the NIH Clinical Center's Department of Bioethics. Before that, for almost a decade I was on the faculty of the University of Kansas and chaired the Institutional Review Board (IRB) at the University of Kansas Medical Center. I have also been a faculty fellow in bioethics at Harvard University and at the University of Chicago. I am pleased to appear before you to discuss the HHS regulations for protection of human subjects, particularly as they relate to OHRP's assurance and IRB registration processes.

OHRP is the component within HHS that is charged with enforcing the Department's protection of human subjects regulations at 45 CFR part 46. OHRP protects the rights, welfare, and well-being of subjects involved in research conducted or supported by HHS by working to ensure that such research is carried out in accordance with those regulations. The codification of human subject protections spans over three decades. On May 30, 1974, the then-Department of Health, Education, and Welfare issued the first Department-wide human subjects protection regulations.

The responsibility for human subject protections is one that OHRP, as a regulator, shares with the Food and Drug Administration (FDA), the HHS agencies that fund research, the research institutions that obtain HHS funds to conduct research, the investigators who carry out HHS-

funded research, and the IRBs that review HHS-funded research. All persons and entities with a role in the conduct or management of human subjects research must fulfill their duty to protect human subjects or subjects could be put at undue risk.

Background

The core provisions of the HHS protection of human subjects regulations are found in subpart A of 45 CFR part 46, referred to as the Basic HHS Policy for Protection of Human Research Subjects, and can be divided into three major areas:

- Requirements regarding submission of a written agreement by an institution conducting HHS-funded non-exempt human subjects research that it will comply with all requirements of the regulations. These agreements are called "assurance" agreements;
- Requirements regarding the review of research, before any subject can be enrolled in a research study, by an IRB; and
- Requirements regarding the actual conduct of the research, including obtaining and documenting of the informed consent of human subjects involved in research, and continuing review by the IRB.

By providing independent ethical review of research, the IRB plays a central role in ensuring that the rights, safety, and welfare of human subjects are adequately protected. The HHS protection of human subjects regulations require IRBs to possess the professional competence necessary to

review specific research activities, and to be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB must also be sufficiently qualified through the experience, expertise, and diversity of its members to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

Before an IRB may approve research under the HHS regulations, it must have sufficient expertise and information to ensure, among other things, that risks to subjects are minimized, risks to subjects are reasonable in relation to anticipated benefits, and that selection of subjects is equitable. Knowledge about the research institution and the qualifications of the investigators that will carry out the research are important considerations in the IRB's assessment.

The IRB also must ensure that the research includes adequate provision for obtaining and documenting the informed consent of the subjects, except in limited circumstances where the IRB may waive these requirements. These informed consent provisions are designed to allow potential subjects to be made fully aware of the following, among other things:

- The purpose of the research, the expected duration of the subject's participation, the procedures to be followed in the research, and identification of any procedures that are experimental;
- Any reasonably foreseeable risks or discomforts;
- Any reasonably expected benefits to the subjects or to others;

- Appropriate alternative procedures or courses of treatment, if any, that may be advantageous to the subjects.

Over the years, HHS has adopted additional research protections for various populations considered to be particularly vulnerable. These are in addition to the basic protections for human subjects in subpart A. The additional protections include:

- Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research (codified at Subpart B of the regulations);
- Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects (codified at Subpart C); and
- Protections for Children Involved as Subjects in Research (codified at Subpart D).

Additional Human Subject Protection Regulations

There are additional federal regulations relating to the protection of research subjects beyond those which are administered by OHRP. In particular within HHS, the FDA has its own set of regulations that apply to clinical trials involving products regulated by FDA. These regulations are substantially similar to 45 CFR part 46 with respect to IRB review, informed consent, and the protections for children involved as subjects in research, but they differ some other respects.

In 1991, fourteen other Federal departments and agencies joined HHS in adopting a uniform set of regulations that are identical to subpart A of 45 CFR part 46. This uniform set of regulations

is known as the Federal Policy for the Protection of Human Subjects, also referred to as the "Common Rule." Two other federal entities, the Central Intelligence Agency and the Department of Homeland Security, must comply with all parts of 45 CFR part 46. For all participating Federal departments and agencies the Common Rule outlines the basic provisions for IRBs, informed consent, and assurances of compliance.

Organization of OHRP

OHRP provides leadership in the protection of human subjects participating in research conducted or supported by HHS by providing clarification and guidance, developing educational programs and materials, and maintaining regulatory oversight. OHRP is organized into three functional Divisions: Compliance Oversight, Education and Development, and Policy and Assurances. In addition, there is the Office of the Director.

OHRP's Division of Compliance Oversight evaluates written substantive indications of noncompliance with the HHS protection of human subjects regulations. OHRP typically asks the institution involved to investigate the allegations and to provide OHRP with a written report of its investigation. OHRP then determines what, if any, regulatory action needs to be taken to protect human research subjects. OHRP's compliance oversight determination letters are posted on its website.[1] OHRP also conducts on-site evaluations at research institutions, in response to indications of possible serious noncompliance. In addition, OHRP conducts not-for-cause

[1] http://www.hhs.gov/ohrp/

evaluations of institutions.

The Division of Education and Development provides guidance to individuals and institutions conducting HHS-supported human subject research; conducts national and regional conferences; participates in professional, academic, and association conferences; and develops and distributes resource materials in an effort to improve protections for human research subjects. The Division also helps institutions assess and improve their human research protection programs through quality improvement consultations.

The Division of Policy and Assurances prepares policies and guidance documents and interpretations of requirements for human subject protections and disseminates this information to the research community. The Division also administers the assurances of compliance and implements the IRB registration process.

Within the Office of the Director, OHRP has established an International Program that provides training to institutions involved in international research to help ensure that ethical protections are afforded to those who participate in research outside the United States, as well as quality improvement assurance consultations to international institutions. In addition, OHRP provides technical and logistical support to the Secretary's Advisory Committee on Human Research Protections (SACHRP), and OHRP's director serves as the Executive Secretary to SACHRP. SACHRP advises the HHS Secretary on issues of human subject protections. The OHRP director also co-chairs the interagency Human Subjects Research Subcommittee whose

membership includes representatives of all the Common Rule agencies, and which reports to the Committee on Science of the National Science and Technology Council (NSTC). Chaired by the President, NSTC is a Cabinet-level Council that serves as the principal means within the executive branch to coordinate science and technology policy across diverse entitites that make up the Federal research and development enterprise.

The Assurance Process

The regulations at 45 CFR part 46 require institutions that are engaged in human subjects research conducted or supported by HHS to file with OHRP an assurance of compliance with the HHS human subjects protection regulations. In particular, the institution is agreeing that all research that is funded by the Department will be conducted in compliance with certain ethical principles and in compliance with the HHS protection of human subjects regulations. In addition, through its assurance, a domestic institution may voluntarily commit to extend these protections to all its human subjects research, regardless of funding source. Many institutions choose to do so.

The assurance must be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by the HHS protection of human subjects regulations. Assurances for HHS-conducted or –supported research must include designation of one or more IRBs that will review the research covered by the assurance.

The institution that is seeking an assurance or already holds an assurance has a responsibility to ensure that the IRBs designated in its assurance are appropriately constituted to review and approve human subjects research covered by the institution's assurance. The institution submitting or holding an assurance is best positioned to assess whether the IRBs it designates possess the competence and expertise necessary to review the research that the institution expects to conduct.

The Federalwide Assurance (FWA) was introduced in 2000 and has been the only type of assurance accepted by OHRP since 2005. Prior to 2005, OHRP and its predecessor, the Office for Protection from Research Risks (OPRR), accepted several types of assurances, including general assurances, cooperative project assurances, multiple project assurances, and single project assurances. The procedures relating to the creation of these documents often involved lengthy discussions with institutions. In 1998, the HHS Office of Inspector General issued a report, *Institutional Review Boards: A Time for Reform*, concluding that this process for obtaining an assurance could be improved. The current largely automated system for processing FWAs was implemented as a response to that OIG Report.

OHRP approves FWAs for federalwide use, which means that other Federal departments or agencies that have adopted the Common Rule may rely on the FWA for research that they conduct or support. Most of these Federal entities accept the FWA, although a few approve their own assurances for some of the research that they conduct or support.

The FWA system, consistent with the OIG recommendations, provides a simplified assurance process that replaces the prior assurance mechanisms used by OHRP, which were more complicated and burdensome than the FWA. Institutions submitting a new FWA may submit all information for initial FWAs, or updates and renewals of existing FWAs via the internet using an interactive page on the OHRP website, with the signature of the Signatory Official submitted on via mail or facsimile.

OHRP generally approves all FWA applications that include the required information that is collected on the OMB-approved FWA form (OMB No. 0990-0278). Required information includes the legal name and location of the institution filing the FWA; a list of components over which the institution submitting the FWA has legal authority that operate under a different name and any alternate name under which the institution operates; a list of the IRBs, by name and registration number, that are to be designated under the FWA; and the names of, and contact information for, the human protection administrator (the person who can serve as primary point of contact for the institution's system for protecting human subjects) and the signatory official (the institutional official legally authorized to represent the institution). The signatory official must sign the FWA and has the responsibility to assure that human subjects research to which the FWA applies is conducted in accordance with the terms of the agreement.

With the adoption of the FWA system in 2000, OHRP's process for reviewing FWAs has been

streamlined and simplified, resulting in a significant reduction in administrative burdens both for institutions submitting assurances to OHRP and for OHRP. Submission of an IRB membership list has always been a component of every type of assurance approved by OPRR and OHRP, as well as assurances approved by other federal departments and agencies that adopted the Common Rule. However, one prerequisite that was implemented by OHRP with adoption of the FWA in 2000 is that any IRB designated under an FWA first must be registered with OHRP. The process for registering an IRB with OHRP is separate from the process of obtaining an OHRP-approved FWA. The IRB registration process includes submission of an IRB membership list.

Currently there are more than 10,000 OHRP-approved FWAs; of these, 76 percent are FWAs for U.S. institutions and 24 percent are FWAs for international institutions.

IRB Registration Process

The OHRP IRB registration process was first developed in 2000 in response to another recommendation from the 1998 OIG Report. In recommending this new system, the OIG was specifically concerned about the possibility that it might become an inappropriate burden to the research process. The Report accordingly made it clear that all that was needed was "a simple registation system in which IRBs regularly update the Federal government on minimal descriptive information" such as location and contact information. The registration system would, among other things, enable OHRP and the FDA to communicate more effectively with

IRBs and thus provide improved protections to human research subjects.

The IRB registration process was also designed to collect information required under the HHS human subjects protection regulations at 45 CFR 46.103, including a list of IRB members (IRB roster) identified by name, qualifications, and affiliations. The IRB registration process was also designed to collect additional information to be provided voluntarily by institutions or IRBs regarding the accreditation status of the institution or IRB organization, total numbers of active research protocols reviewed by the IRB (including protocols supported by other Federal departments or agencies) and the nature of those protocols, and IRB staffing.

Recently, on January 15, 2009, OHRP issued a new IRB registration final rule that will require submission of some of the information that was being submitted voluntarily (e.g., approximate number of all active protocols and those conducted or supported by HHS, and the approximate number of full time equivalent positions). FDA also issued an IRB registration final rule on January 15, 2009 that creates new requirements for IRBs in the U.S. that review clinical investigations that are regulated by FDA. OHRP's and FDA's IRB registration rules are compatible and largely harmonious, and will be implemented through a single registration system that will be accessible through the OHRP website. That web-based IRB registration system is being designed to be largely automated, so that little staff time will be required for the acceptance of IRB registration applications.

Organizations registering new IRBs or updating or renewing already registered IRBs may submit all information via the internet using an interactive page on the OHRP website. Beginning on July 14, 2009, the effective date of OHRP's IRB registration rule, each IRB that is covered by the HHS regulations for the protection of human subjects must be registered electronically, unless an institution or organization lacks the ability to register its IRB(s) electronically. In such a case, the organization must send its IRB registration information in writing to OHRP.

OHRP generally accepts all IRB registration applications that include the required registration information that is collected on the OMB-approved IRB Registration form (OMB No. 0990-0279). Required information includes: the name and mailing address of the institution operating the IRB; name of, and contact information for, the institution's or organization's head official; each IRB chairperson's name and contact information; and the IRB roster that includes, for each member, their name, gender, degree, a designation of whether their area of concern is in a scientific or nonscientific area, and a designation of whether they are affiliated or not affiliated with the institution that is registering the IRB.

When reviewing an IRB membership list in the context of IRB registration, OHRP ascertains that the IRB satisfies the following minimum requirements of the HHS regulations on protection of human subjects at 45 CFR 46.107:

- there are at least five members listed;
- at least one member is designated as having primary concerns in scientific areas;

- at least one member is designated as having primary concerns in nonscientific areas; and
- at least one member is designating as being not otherwise affiliated with the institution registering the IRB.

Currently there are more than 6,000 IRBs registered with OHRP. Of that number, 60 percent are IRBs that are located in the U.S. and 40 percent are IRBs that are located abroad.

OHRP makes information collected in the IRB Registration System and the FWA system available to other Federal departments and agencies that have adopted the Common Rule and that find that a FWA is appropriate for the human subjects research they conduct or support. The information enables these entities to confirm that a particular institution holds an applicable assurance approved for Federalwide use (i.e., that it has agreed to be bound by the applicable regulations) and identify an institution's designated IRB(s) before making an award to that institution to support research involving human subjects.

Conclusion

Through this system of assurances of compliance, IRB review, and informed consent, the HHS regulations are designed to protect the rights and welfare of human subjects, while enabling the conduct of important, ethical research. The protection of human subjects in research studies is a priority for the Department, and it is the mission of OHRP to support, strengthen and provide leadership to the nation's system for protecting research subjects who participate in research that is conducted or supported by HHS.

Thank you for this opportunity to present this information to you. I would be happy to answer any questions you may have.