Trends in Oversight of Human Research Protections?

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Protection of Human Subjects?

☐ Ethical Principles
☐ Ethical Review
  ■ Institutional review boards
☐ Responsible conduct
  ■ Well-trained and well intentioned investigators
☐ Regulations
  ■ One cannot legislate good behavior
Regulations, to what end?

- An attempt to translate ethical principles to effective practices
- Not all nations have adopted a regulatory approach; some may be better off than the US
- Regulations do not protect the interest and well-being of human subjects in research
- The long-standing and current focus on regulatory compliance has diverted attention and resources from effective efforts to actually protect human subjects in research

Why Compliance?

- Policies, rules and regulations are intended to promote responsible conduct
- Compliance is a minimal requirement
- Protecting the safety and well-being of human subjects in research is the goal
- Compliance is essential
- Compliance does not achieve the goal
HHS Regulations for the Protection of Human Subjects in Biomedical and Behavioral Research

- HHS human subject protection regulations at 45 CFR part 46 were first issued in 1974.
- In 1978, the National Commission or the Protection of Human Subjects of Biomedical and Behavioral Research published “Ethical Principles and Guidelines for the Protection of Human Subjects of Research,” also known as the Belmont Report.
- The Belmont Report identifies three fundamental ethical principles for all human subjects research: respect for persons, beneficence, and justice.

HHS Regulations for the Protection of Human Subjects in Biomedical and Behavioral Research

- The current version of the regulations includes five subparts:
  - Subpart A is the basic set of protections for all human subjects of research conducted or supported by HHS, and was revised in 1981 and 1991, with technical amendments made in 2005.
  - Three of the other subparts provide added protections for specific vulnerable groups of subjects.
  - Subpart B, issued in 1975, and most recently revised in 2001, provides additional protections for pregnant women, human fetuses, and neonates involved in research.
  - Subpart C, issued in 1978, provides additional protections pertaining to biomedical and behavioral research involving prisoners as subjects.
  - Subpart D, issued in 1983, provides additional protections for children involved as subjects in research.
  - Subpart E, issued in 2009, requires registration of institutional review boards (IRBs) which conduct review of human research studies conducted or supported by HHS.
The Food and Drug Administration (FDA) is an HHS agency that regulates clinical investigations of products under its jurisdiction, such as drugs, biological products, and medical devices.

FDA regulations are published in title 21 of the CFR.

FDA’s human subject protection regulations include:
- 21 CFR part 50, Protection of Human Subjects
- 21 CFR part 56, Institutional Review Boards
- 21 CFR part 312, Investigational New Drug Application
- 21 CFR part 812, Investigational Device Exemptions


Subpart D was added to 21 CFR part 50 in 2001 and provides additional protections for children involved in clinical investigations.


Other FDA regulations that apply to clinical investigations include 21 CFR part 54, Financial Disclosure by Clinical Investigators.
OHRP Recent Developments

Recent News:
- December 1, 2010 Guidance on IRB Continuing Review of Research
- December 1, 2010 Guidance on IRB Approval of Research with Conditions
- October 14, 2010 Revised Frequently Asked Question Regarding Engagement in Research
- October 4, 2010 Clarification of "noninvasive" in expedited review category 3
- September 21, 2010 Guidance on Withdrawal of Subjects from Research

Guidance on IRB Continuing Review of Research

- Focus on new information
- May request monitoring reports
- Adequacy of informed consent process
- Investigator and institutional issues
- Evaluate research progress
- Expirations not suspensions
Guidance on IRB Approval of Research with Conditions

- Approval with conditions does not require full board acceptance of meeting those conditions
- Verification of conditions is not an expedited review
- IRB has the authority to require changes
- IRB may “table” the study

Revised Frequently Asked Question Regarding Engagement in Research

- An institution is generally considered to be engaged in human subjects research when its employees or agents obtain the informed consent of human subjects.
- The statement that pertained to awardee institutions bearing the ultimate responsibility for protecting subjects involved in the research conducted under the award, even when all human subjects activities are carried out by other institutions has been removed.
Clarification of "noninvasive" in Expedited Review Category 3

- How far in can you go without being invasive?
  - Vaginal swabs that do not go beyond the cervical os;
  - Rectal swabs that do not go beyond the rectum; and
  - Nasal swabs that do not go beyond the nares.

Guidance on Withdrawal of Subjects from Research

- Subject withdraws – no more intervention or obtaining PHI
- Subject partially withdraws – no more primary intervention, but may obtain PHI, or secondary interventions
- PI terminates a subjects participation – may follow up with PHI
- Data – FDA requires it to be maintained
Additional Informed Consent Element in FDA Studies

- Informed consent documents for drug or device trials must include a specific statement that clinical trial information will be entered into a databank
  - Effective date - March 7, 2011
  - Compliance Date – March 7, 2012

Research with Decisionally-Impaired Subjects

- §46.116 General requirements for informed consent.

- Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.
Policies & Procedures for Decisionally-Impaired Subjects

- Investigator Responsibilities
  - IRB Approval
  - Determination of Incapacity
  - Identification of Surrogate
  - Obtaining Surrogate Consent/ Subject Assent
  - Periodic Reevaluation of Ability to Consent
  - Documentation

- IRB Responsibilities
  - Make sure study meets state eligibility requirements
  - Ensure consent documents contain all additional elements
  - Continuing review as required by risk
Policies & Procedures for Decisionally-Impaired Subjects

- Application Addendum
- Determination of Capacity
- Surrogate Self-Certification
- Consent and Assent Form Templates
- Consent form for individuals regaining the capacity to consent

Title 21 Sec. 50.25 (C):
Elements of informed consent.

c) When seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement shall be provided to each clinical trial subject in informed consent documents and processes. This will notify the clinical trial subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act.

The statement is: “A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.”
Title 21 Sec. 50.25 (C): Elements of informed consent.

- Language must be included in translated “short form” consent documents
- Only if clinical investigations were initiated on or after the compliance date
- Reaffirmation of consent is not necessary
- Only required if the clinical trial is an “applicable clinical trial”
- Not required to be in a specific section of the form

What’s that in the road, a head?

- Our approach to regulation and oversight of human research and protection of human subjects is being challenged as never before, as stakeholders across the board question its merits and effectiveness.
- The need to promote responsible conduct of research and to ensure that the interests and well-being of research participants are respected have changed and need to move beyond our ineffective, counterproductive focus on regulatory compliance with procedural requirements.
In 1991, the “Federal Policy for the Protection of Human Research Subjects,” informally known as the “Common Rule” was issued by 15 federal departments and agencies. The Common Rule was based on the HHS 45 CFR part 46 subpart A, and includes identical language in the separate regulations of those departments and agencies. Technical amendments were made to the Common Rule in 2005. One additional agency (the Central Intelligence Agency) is required to follow the Common Rule by executive order, and one additional department (the Department of Homeland Security) chose to follow all HHS subparts. Other departments and agencies have adopted one or more of the other HHS subparts and some have their own additional human subject protection regulations.

“The heads of other Common Rule departments and agencies may independently reach different conclusions about which, if any, procedural standard(s) to accept as providing protections at least equivalent to the Common Rule. This is among the reasons that multiple procedural standards are included on the FWA form for international (non-U.S.) institutions, which may be relied upon by all Common Rule departments and agencies.”
The So-Called Federalwide Assurance

☐ The Federalwide Assurance exists only in name
☐ There is no such thing as a true Federalwide assurance in practice
☐ Although all of the signatory agencies have adopted the “Common Rule’, the provisions may be interpreted and enforced as deemed most appropriate by each agency, and they may add their own provisions.

“Unchecking the box?”

☐ A mechanism used by institutions to limit government oversight of their human subjects research
☐ The procedure specifically limits OHRP’s jurisdiction for oversight and intervention
☐ By limiting oversight authority, there is less at risk in the event of serious non-compliance.
☐ The approach takes advantage of the inconsistencies and loopholes in the regulatory framework to avoid strong and effective oversight
☐ The impact on protection of human subject, if any, is unknown
SACHRP

- Replaced the National Human Research Protections Advisory Committee
- Advises the Secretary of Health and Human Services
- Currently has two active Subcommittees

Subcommittee on Harmonization

- The Subcommittee will identify and prioritize areas in which regulations and/or guidelines for human subjects research adopted by various agencies or offices within HHS would benefit from harmonization, consistency, clarity, simplification and/or coordination.
- The Subcommittee will then develop recommendations, for consideration and possible adoption by SACHRP, to harmonize and simplify these guidelines and regulations.
- The goal of this subcommittee effort is to reduce unnecessary burdens on research efforts, thus resulting in better allocation of research resources and promoting the safety and welfare of human subjects.
Subcommittee on Federal Policy for the Protection of Human Subjects (Subpart A)

- To review and assess all provisions of subpart A of 45 CFR part 46 and relevant OHRP guidance documents.
- Based on its review and assessment, the Subcommittee will develop recommendations for consideration by SACHRP on the following topics and the goals of enhancing protection of human subjects and of reducing regulatory burdens that do not contribute to the protection of human subjects:
  - (1) recommendations on the interpretation of specific Subpart A provisions;
  - (2) recommendations for the development of new, or modification of existing OHRP guidance; and
  - (3) recommendations regarding possible revisions to subpart A

Equivalent Protections—No!

- “HHS clarifies that the requirements of HHS regulations must be satisfied for all HHS-conducted or -supported research covered by an FWA, regardless of whether the research is conducted domestically or internationally.”
- “To date, HHS has not deemed any other procedural standards equivalent to the protection of human subjects.”
Hot Spots

IRB Lacks Sufficient Information to Make Determinations Required for Approval of Research

“The IRB, when reviewing protocol applications, lacked sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, the IRB reviewed insufficient information regarding (a) risks to subjects and how they are minimized; (b) subject recruitment and enrollment procedures; (c) the equitable selection of subjects; (d) provisions to protect the privacy of subjects and maintain the confidentiality of data; and (e) additional safeguards to protect the rights and welfare of subjects who are likely to be vulnerable.”

Hot Spots

Evaluating Investigator and Institutional Issues

- When appropriate, the reviewing IRB should consider issues regarding the investigator and the institution(s) where the research is being conducted during its review, such as the following:
  - The investigator’s situation or qualifications (e.g., suspension of hospital privileges, change in medical license status, or increase in number of research studies conducted by the investigator);
  - Evaluation, investigation, and resolution of any complaints related to the investigator’s conduct of research;
  - Acceptability of the proposed research in terms of institutional commitments (e.g., personnel and financial resources, adequacy of facilities) and applicable regulations, State and local law, or standards of professional conduct or practice; and
  - Reports from any third party observations of the research carried out under 45 CFR 46.109(e).
Hot Spots

Where does the buck stop?

HHS regulations at 45 CFR 46.103(c) require that an institution’s assurance of compliance with the regulations for the protection of human subjects shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by the regulations.

The Growing Backlash against Compliance as a Goal

- Regulatory oversight of human research and IRB review is provoking an "allergic reaction"
- Increasingly, the current approach is viewed by the research community, industry and the government as an impediment to research and to commerce.
- OHRP and FDA are likely to have fewer resources and diminished oversight capacity in the future.
Where do we go from here?

- The future of oversight of human research and protection of human subjects is likely to change as efforts to limit the size of government diminishes its effectiveness.
- The need to promote responsible conduct of research and to ensure that the interests and well-being of research participants are respected will persist.

Professionalism is the key…

- What government cannot do will be done by private-third parties using the tools of professionalism
- Mandatory training and education
- Examination-based certification of competency
- Accreditation of programs and sites
What will drive change?

- A well-educated public
- Continuing interest in improving health and well-being, both for patients and for corporate bottom lines
- Legal action against offenders
  - Institutional liability concerns
  - Economic-based quality and safety incentives

Thanks for listening!

Questions and/or Comments?