FDA Update
New Expectations for IRBs

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DHHS/FDA Regulations
Additional Protections for Children

DHHS/FDA

- **Subpart D – Children as Subjects in Research**
  - **FDA Effective April 30, 2001 for new studies**
  - **45 CFR 46.401 – 409/21 CFR 50.50 - 56**

DHHS/FDA Regulations
Additional Protections for Children

Definition of Children

- Children are persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations as determined under the applicable law of the jurisdiction in which the research will be conducted.
- This provision means that the local law at the site of the research will determine the legal age of consent of the participants.

45 CFR 46.402(a) 21 CFR 50.3 (o)

Subpart D
Additional Protections for Children

Additional Duties of IRB

Find (decide) and Document

- **Permitted research involving children**
  - **Four categories based on risk to children and anticipated benefit to the individual child**
- **Permission (consent) of parents and assent by children**
- **Advocate for Wards**

Subpart D
Additional Protections for Children

IRB may determine assent is not required when:

- The child is not capable
  - age
  - maturity
  - psyche state
- The prospect of direct benefit important to health or well-being of children and available only in this study

45 CFR 46.108(a)
21 CFR 50.55(c)

Subpart D
Additional Protections for Children

Permission of the Child's Parents

- DHHS allows waiver of parental permission under specified conditions
  - permission not a reasonable requirement, e.g.,neglected or abused children

45 CFR 46.408(c)

FDA has not adopted this provision

Subpart D
Additional Protections for Children

Documentation of IRB Decisions

- In meeting minutes
- In letter to investigator
- Copy to sponsor (not required by regulation; depends on relationship IRB has with the sponsor)

Subpart D
Additional Protections for Children

Documentation of IRB Decisions

- Level of risk
- Whether assent is required
- If so, whether documentation of assent is required, and if so, how
- If permission of one or both parents is waived (no FDA waiver)

ICH

- FDA – extent to which confidentiality will be maintained and notes FDA may inspect the records
- ICH – monitors, auditors, the IREB/IEC, and regulatory authorities will be granted direct access to records. The subject is authorizing such access by signing the informed consent form
- ICH – records will be kept confidential, and will not be made publicly available

FDA 21 CFR 50.25(a)(5)
ICH 4.8.10(n)
ICH 4.810(o)

ICH

- FDA – No corresponding section except pedes
- ICH
  - The subject's responsibilities
  - Subjects enrolled with consent of legally acceptable representative should assent, sign and date the written informed consent
  - Subjects of non-therapeutic trials should personally give consent unless objectives of trial cannot be met

ICH 4.8.10(a)
ICH 4.8.12, 13, 14

ICH

- FDA – copy given to subject not required to be the signed and dated copy
- ICH – subject should receive a copy of the signed and dated consent, other written information, updates, amendments

FDA 21 CFR 50.27(a)
ICH 4.8.9

ICH

- FDA – witness to the oral presentation, signs consent or short from and narrative
- ICH – if unable to read, an impartial witness should be present during the entire discussion
- ICH – witness should sign and personally date the consent. Witness attests the info was accurately explained to, and apparently understood by, the subject and the consent was freely given

FDA 21 CFR 50.27(b)(2)
ICH 4.8.9

ICH

- FDA – No specific corresponding section
- ICH – IRB/IEC may be asked to provide copies of its written procedures and membership lists
- ICH – IRB/IEC should consider the qualifications of the investigator, e.g., CV
- ICH – IRB/IEC should review amount and method of payment to subjects

ICH 3.4
ICH 3.1.3
ICH 3.1.8

IRB Registration

and

OHRP Assurance Process

Why Have IRB Registration?

- IRB registration is intended to rectify two apparent deficiencies:
  1. Exact count of IRBs
  2. Ease of notification of IRB news
- It also identifies:
  1. IRB Chair
  2. Human protections administrator

IRB Registration

- Location
  - http://ohrp.osophs.dhhs.gov/irbasur.htm
- You need to list:
  - Head official of organization
  - IRB chairperson and membership for each IRB

Prisoners in Research
Subpart C

- Applies when a subject is or becomes a prisoner
- If a subject becomes a prisoner, research continues but the following must be done:
  - PI notifies the IRB
  - IRB reviews protocol at earliest convenience

http://ohrp.osophs.dhhs.gov/humansubjects/guidance/prison.htm

Compliance Activities and Concerns

Ethical Principles

- Are these just bureaucratic rules of DHHS and FDA?
- Does record keeping matter?

Record Keeping

- Corrlelation between inability to maintain records and inability to protect the rights and welfare of study subjects
- If it is *not* documented, it *didn't* happen (not exactly true…but often said)

Research at Rush Suspended


Chicago Tribune

Rush halts its research on humans

October 27, 1998

Research at Duke Suspended

The Washington Post

U.S. Halts Research On Humans at Duke

University Can't Ensure Safety, Probers Find

May 12, 1999

Research in Oklahoma Suspended

The Washington Post

U.S. Halts Cancer Tests In Oklahoma

Patient Protections Ignored, Agency Says

July 11, 2000

The New York Times.

Research at (your name here) suspended

FDA RESTRICTED LIST FOR CLINICAL INVESTIGATORS

- Clinical investigators who have agreed to certain restrictions with respect to their conduct of clinical investigations
- Where restrictions have been removed, it is so noted in the comments column

The List to Avoid

http://www.fda.gov/ora/compliance_ref/bimo/restlist.htm

FDA DISQUALIFIED/TOTALLY RESTRICTED LIST FOR CLINICAL INVESTIGATORS

- Investigators who have been disqualified or "totally restricted"
- A disqualified clinical investigator is not eligible to receive investigational drugs, biologics, or devices
- Where an investigator has been reinstated it is so noted

The List to Avoid

http://www.fda.gov/ora/compliance_ref/bimo/disqlist.htm

FDA DEBARRED LIST

- Individuals or firms barred from participating in the drug industry because they have been convicted of crimes related to FDA's regulation of generic drugs.

Sections 306(a) and (b) of the FD&C Act

The List to Avoid

http://www.fda.gov/ora/compliance_ref/debar/default.htm

Informed Consent

Not just review of the paper form anymore

- Consent before involvement
- Opportunity to consider
- Minimize coercion and undue influence
- In language understandable to subject
- No waiver of rights
- No release from liability
- Interview conducted by qualified person

HHS 45 CFR 46.116

FDA 21 CFR 50.20

Guidance

NCI Informed Consent Guidance

http://cancer.gov/clinical_trials/conducting

- Scroll to: Participants in clinical trials
- Click on: A guide to understanding informed consent
- Click on: digest page
- Click on: simplification of informed consent documents
- Recommendations
- Forms
  - Sample Consent Form: Phase 2 … trial
  - Sample Consent Form: Phase 3 … trial

HIPAA

Health Insurance Portability and Accountability Act of 1996

Privacy Rule Compliance Date
April 14, 2003

- Not HIPPA
- Not “Health Information”

HIPAA - Protects the data

Rules to protect the privacy and confidentiality of the individually identifiable health information

HHS and FDA - Protects the people

Rules to protect the rights and welfare of human participants in research studies

- **Protected Health Information (PHI)**
  Individually identifiable health information
- **Treatment, Payment, or Operations (TPO)**
- **Covered entity – does TPO and bills insurance**

Education and Quality Improvement are considered part of "Operations"

Research is neither "Operations" nor "Marketing." It is a separate category

Research Use or Disclosure of PHI

- Authorization by the study subject
- Waiver of Authorization by IRB/PB
- Review preparatory to research
- PHI of decedents

- De-identified data (no longer contains PHI)
- Limited data set

Authorization by the Prospective Study Subject

- Authorization required to use and disclose PHI
  - Default position for prospective studies, unless not feasible
- Informed consent required by HHS/FDA
- Single authorization document allowed for all uses and disclosures, including research
- HIPAA authorization may be combined with any other legal permission e.g., informed consent
- Patients must be given a signed copy of the authorization agreement

Revocation of Authorization

Early withdrawal from the study

- HHS/FDA withdrawal process does not change
  - Can be oral
- HIPAA revocation of authorization
  - Must be in writing to the PI

Waiver of Authorization by IRB/PB
Three Criteria

1. No more than minimal risk to the privacy of individuals
2. Not practicable to conduct the research without the waiver or authorization
3. Not practicable to conduct the research without access to and use of the PHI

Review Preparatory to Research

- Use or disclosure is sought solely to review data to prepare a research protocol or similar purposes preparatory to research
- No PHI removed from covered entity
- Review of PHI is necessary for the research purposes

Definition of "Human Subject”

- HIPAA includes deceased subjects
- DHHS does not
- FDA does not

An [living] individual about whom an investigator...conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

PHI of Decedents

- No authorization or waiver required
  - Permission of family members may be required, but this is not a HIPAA issue

Is the IRB a Business Associate?

Is a Business Associate Agreement needed?

- Is PHI routinely used by or disclosed to the IRB?
- If so, is the transaction covered by another HIPAA pathway?
- The contract should describe all anticipated transfers of PHI to the IRB
- No BAA needed between researcher and covered entity
- Sponsors claim they are not Business Associates

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De-Identification

- When all listed identifiers removed
  - (list of 18 identifiers)
- Then no authorization or IRB/PB waiver is required

De-Identification

18 identifiers

- Names
- Geography smaller than a state
- All dates except year
- Telephone numbers
- Fax numbers
- Email addresses
- Social security numbers
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- Certificate/license numbers
- VIN, license plate numbers
- Device serial numbers
- Web Universal Resource Locators
- Internet protocol (IP) numbers
- Biometric ID, e.g., finger, voice prints
- Full face photos
- Any other unique identifying number

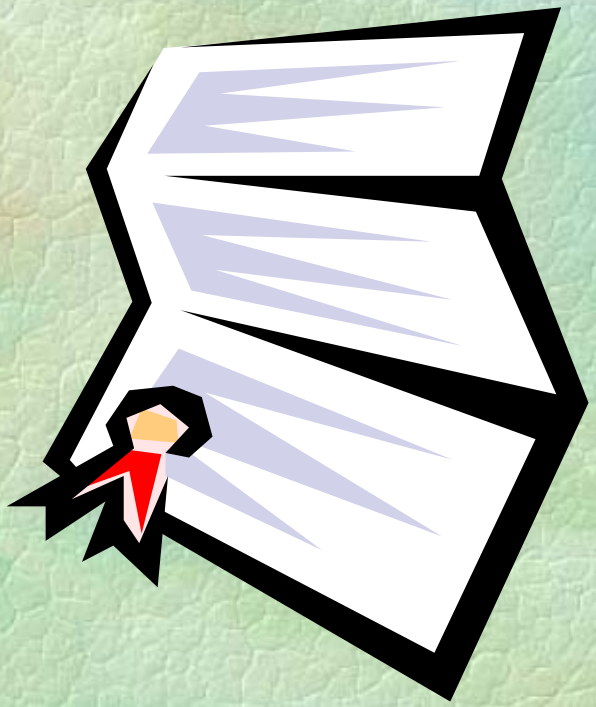
Limited Data Sets (LDS)

- Stripped of all direct identifiers:
  - name
  - street address
  - phone
  - e-mail
  - social security numbers
  - medical record numbers
  - health plan numbers
  - device serial numbers
  - biometric identifiers,
    e.g., fingerprints, full-face photographs

Limited Data Sets (LDS)
(cont'd)

- Allows use and disclosure of all identifiers not prohibited, e.g.:
  - dates of hospital admissions and discharges
  - dates of birth and death
  - zip code, state, county, city, precinct, etc.
  - only minimum necessary should be disclosed
- Need a Data Use Agreement
- Between covered entity and the data recipient

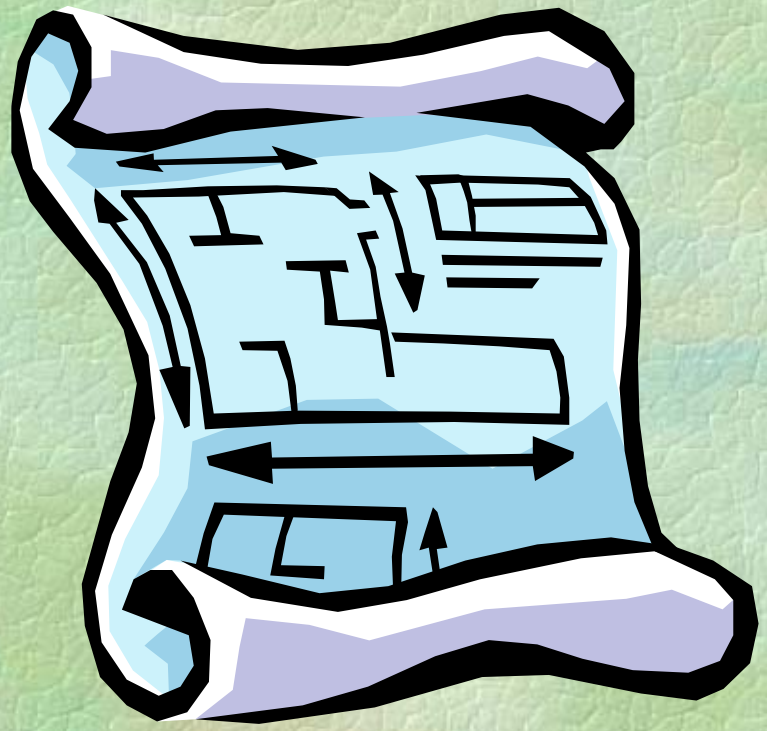
ACCREDITATION



Accreditation

AAHRPP The Association for the Accreditation of Human Research Protection Programs
http://www.aahrpp.org/

NCQA National Committee for Quality Assurance
http://www.ncqa.org/



HRPP

Human Research Protection Plan

HRPP Training

- OHRP requirements
  - Initial training: OHRP training module

    http://ohrp.osophs.dhhs.gov/irbasur.htm

- NIH requirements
  - Training of principal investigators receiving NIH funding

    http://ohsr.od.nih.gov/
    Click on “training,” “researchers

Overarching Concerns

- Is there a "culture of subject protection"?
- Does the institution support and respect the IRB and its mission?
- Are IRB members and investigators and IRB staff knowledgeable about regulatory requirements?
- Is there adequate documentation of IRB findings and actions?

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