Introduction to the Human Investigation Committee and its processes

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Chair, HIC-1

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YALE UNIVERSITY
School of Medicine
Objectives

- Introduce the IRB world
- Review definitions, references and resources
- Review HIC policies and processes
- Review special considerations in doing research with human subjects
Terminology and Regulatory Definitions

- **CFR**: Code of Federal Regulations (Federal law)
- **IND**: Notice of claimed investigational exemption for a new drug (FDA-1571). Includes a detailed description of planned investigations, submitted to FDA.
- **IRB**: Institutional Review Board. At Yale, referred to as HIC (Human Investigation Committee).
- **Minimal Risk**: probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during performance of routine physical or psychological exams or tests.
Terminology and Regulatory Definitions

- **Research**: a systematic investigation designed to develop or contribute to generalizable knowledge.

- **Research subject**: a living individual about whom an investigator obtains data through intervention or interaction, or identifiable private information.

- **HIPAA**: Health Insurance Portability and Accountability Act. Establishes conditions under which protected health information (PHI) can be used within an institution and disclosed outside it; requires that we maintain privacy and security of PHI.
IRBs at Yale University

- Human Investigation Committees (HIC I and HIC II) serve YNH Medical Center & Research Affiliates
- Human Subjects Research Review Committee (HSRRC) serves the School of Nursing
- Human Subjects Committee serves the Faculty of Arts and Science (FAS)
HIC Staff

- Executive Director, Maurice (Jeremiah) Mahoney, M.D., J.D. and Chairman HIC II
- Chair, HIC I, Sandra L. Alfano, Pharm.D., CIP
- Deputy Director, Kathleen Uscinski, CIP, MBA
- Compliance Manager: Tracy Rightmer, J.D.
- Committee Manager: Cathleen Montano, J.D.
- Expedited Review Mgr: Brandy Henriques, CIP
- Education/Outreach Mgr: Jean Larson
- Coordinators: Adamina Roman, MS, Amy Blakeslee, Michael Centola, Ellen Bedard, Katrina Blount, Laurie Baril
- Administrative Staff: Constance Costa, Lori Sena, Kim Miniter
HIC Responsibilities

- All research involving living human subjects
  - At Yale-New Haven Medical Center, EPH, Research Affiliates
  - Use of medical records kept by YNHMC
  - By Yale faculty, employees or students (anywhere)
- Approves, re-approves, defers, approves with specific minor changes, or disapproves (new studies, amendments, re-approvals)
- Handles Adverse Event reports
- Performs Audits/Monitoring, Responds to concerns and complaints, analyzes and reports
- Has discretion to apply sanctions
HIC Responsibilities

- Determines Exempt & Expedited Status
- Endorses another IRB’s approval
- Decides whether or not to accept Research Affiliates
- Manages outsourcing to Centralized IRB (Western)
- Handles study-specific conflict of interest
- Educates investigators, research staff, administrators and HIC members
- Guides research staff in design and revision of protocol and consent
- Provides other guidance, as required
HIC Website

http://info.med.yale.edu/hic/index.html

- HIC guidelines, templates and checklists
- HIC Membership lists
- Forms
- Policies and useful links
Department of Medicine Clinical Investigation

- Helpful Decision trees:
- http://latte.med.yale.edu/ResearchMed/Pages/decisiontreemain.htm
Submissions to HIC

- Application to Involve Human Subjects in Research
- Amendments
  - Administrative
  - Full Committee
- Reapprovals
- AE reports
- DSMB recommendations
- HIPAA RAF
HIC Review procedures

- **Primary Reviewer System (from HIC)**
- **New Protocols**
  - Primary reviewer (selected by the investigator)
  - Secondary reviewer (assigned by the HIC coordinator)
- **Re-Approvals**
  - Reviewer (assigned by the HIC coordinator)
- **Amendments**
  - Reviewer (assigned by the HIC coordinator)
- **Coordinator performs administrative review**
HIC Schedules and Timeframes

- HIC I meets First and Third Wednesday
- HIC II meets Second and Fourth Wednesday
- Every fifth Wednesday is a policy meeting
- Deadline for Protocols is 12 Noon Eight Days Before Each Meeting
- New Protocols meeting Tuesday deadline will be scheduled for the next week’s meeting (providing the primary reviewer sits on that committee)
- Expedited Reviews – 2-4 weeks
- Exemptions – 1-2 weeks
- Office Hours: 8:30 – 4:00
Approval considerations

- Risk: Benefit ratio reasonable?
- Selection of subjects equitable?
- Appropriate informed consent
- Data collected adequately monitored
- Adequate provisions to protect privacy and maintain confidentiality of data
- Risks are minimized?
- Additional safeguards for those who need it (children, prisoners, etc.)
How are the principles applied?

- Careful review of the *protocol*
  - Inclusion/Exclusion Criteria
  - DSMP and Stopping Rules
  - Risks/Benefits
  - Consent *Process*
  - In Case of Injury Section
How are the principles applied?

- Careful review of the consent form
  - Purpose
  - Research Procedures
  - Risks
  - Anticipated Benefits
  - Alternative Treatments
  - Voluntariness
Consent issues

- Informed consent is not only a document.
- It is a process: a dialogue between the researcher and the subject. Information exchange needs to take place before, during, and sometimes after the study.
- Information, comprehension, and voluntariness.
Consent Issues: Information

- Purpose of the research
- Research procedures/expectations explained
- Known (and unknown) risks explained with possible ramifications
- Economic considerations (impact on individual)
- Benefits stated reasonably in relation to phase of protocol
- Alternatives noted to inform decision
Consent Issues: Comprehension

- The manner and context in which information is conveyed are as important as the information itself
- Organized presentation of the material
- Providing sufficient *time* to ask questions and to consider participation
- Investigator getting consent must assure comprehension
Consent Issues: Voluntariness

- Begin with an invitation to participate
- Free of coercion (overt threat of harm)
- Free of undue influence (offer or promise of excessive or improper reward)
- Participant is free to decline or to withdraw at any time without repercussions
 Consent issues

- Be sure that the informed consent process is not misleading
- Benefit is not overstated
- Risk/Benefit ratio is carefully considered
Additional protections

- For those who need them
- Vulnerability of a given population or person sometimes changes
Data and Safety Monitoring Plans

Required by the HIC for all studies

- Explicit statement of risk with rationale
- Adverse event grading and attribution scheme
- Plan for reporting unanticipated serious AEs to whom and when
- Plan for safety and data review
- If applicable, DSMB composition, structure, operations and reporting (recommendations must go to HIC)
Economic Considerations and ICOI

- Inform participants about costs of participation, and payments to made (if any)
- Costs of research should be clearly differentiated from costs of standard care
- Tell them what will happen in case of injury (who will pay)
Other information to subjects

- Ads
- Letters
- Websites

All must be submitted to HIC for review
Expedited Review

• Must be minimal risk
• Must be on ‘the list’
Exempt research

- Determination made by HIC, not PI
- Existing data if publicly available or the information is recorded without identifiers
- If identifiers must be collected, the project is not exempt
Required training

- Human subjects protection training (HSPT)
- Required for all investigators and key study personnel
- These sessions, HIC web link, or NIH web-based training
Special considerations in human subjects research: Vulnerable subjects

- “…vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons…”
- “…additional safeguards have been included in the study to protect the rights and welfare of these subjects.”

Subparts B, C, D
Special considerations in human subjects research: Vulnerable subjects

**Decisionally impaired**

- Assess capacity to consent
- Certain populations may be predisposed to impairment (e.g. brain mets, new devastating diagnosis, etc)
- Precautions in place to add protections, such as surrogate consent, consent monitor, independent evaluator
- Precautions required are tied to risk level of protocol
Special considerations in human subjects research: Vulnerable subjects

Minors

- Categories of approval tied to risk and benefit of the protocol
- 404: no more than minimal risk
- 405: greater than minimal risk, but potential for direct benefit to the subject
- 406: no direct benefit, and only a minor increase over minimal risk and likely to yield generalizable knowledge about subject’s disorder or condition
- 407: not otherwise approvable (refer to DHHS)
Special considerations in human subjects research: Vulnerable subjects

Pregnant women

- Are there adequate provisions for monitoring the informed consent process?
- Is there evidence of prior animal and non-pregnant studies?
- Consideration of risk and benefit to both mother and fetus
- No inducements are offered to terminate pregnancy
Special considerations in human subjects research: Vulnerable subjects

Prisoners

• Prisoners are a vulnerable population because they are under constraint because of their incarceration, and this could affect their ability to make a truly voluntary and uncoerced decision about participation in research.

• 45CFR46, Subpart C specifies special protections.
Special considerations in human subjects research: Vulnerable subjects

Minorities and Non-English speaking

- Principle of Justice: do not overly burden one group, nor exclude a group from potential benefit
- Translation issues
- Issue of ongoing communication (consent process)
Special considerations in human subjects research: Vulnerable subjects

International research

- Whose principles apply?
- Need for local review to evaluate protocol for cultural, political and legal issues
- Issue of Justice, heightened awareness about some sponsors who may use vulnerable foreign populations for risky research with little potential for future benefit
Special considerations in human subjects research: When are DSMBs required?

- Required by NIH for all Phase III trials
- May be appropriate for Phase I or II trials if multiple sites, blinded, high risk, or vulnerable populations
- May be required by HIC when potential for COI exists
- Plan should be commensurate with risks, size and complexity of protocol
Special considerations in human subjects research: Certificate of Confidentiality

- Issued by DHHS to protect the investigators from having to give up study data even under subpoena
- Protective power may be limited as this has rarely been challenged in the courts
- Generally required by HIC when sensitive data (such as drug abuse information) is collected
- Many cooperative group studies have COC in place
Special considerations in human subjects research: Data or tissue banking

- Specify what will be stored, what areas of research may be pursued, how long it will be stored, whether there will be identifiers, and how to go about withdrawing samples
- Potential risks of breach of confidentiality must be specified (threat to insurability, employability, etc)
- Signed consent and HIPAA RAF (separate)
Special considerations in human subjects research: Clinical trials registration

- International Conference of Medical Journal Editors has made registration of certain trials a condition of publication.
- Goal is to increase access to trials, as well as create transparency in access to results (both positive and negative).
- Sponsor or IND holder must register.
- ClinicalTrials.gov is an example of a registry.
Special considerations in human subjects research: HIPAA

- Requires the standardization of electronic patient health, administrative and financial data
- Establishes HIPAA Privacy Rule
  - Conditions under which protected health information (PHI) can be used within an institution and disclosed outside it
  - Grants individuals certain rights regarding their PHI
  - Requires that we maintain the privacy and security of PHI
Special considerations in human subjects research: Multicentered trials

- Regulatory and documentation burden increase if serving as the coordinating center for a multicentered trial.
- Documentation and data management plan (and required resources) should be thought out carefully prior to starting and detailed in the HIC application.
Special considerations in human subjects research: FWA/affiliates

- If HIC is the IRB of record for an affiliated site, this must be included in the FWA.
- Process of education and policy development for research affiliates
- Yale’s FWA currently names 17 research affiliates (such as YNHH, CMHC, Hill Health Center...)
Conclusion

- The HIC is committed to a partnership with the research community in the promotion of safe and ethical research.

- HIC staff and members are available to the research community for consultation, education, and guidance.