Introduction to the Human Investigation Committee

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Objectives

- Introduce the IRB world
- Review definitions, references and resources
- Understand the ethical foundations of human subjects research
- Review HIC policies and processes
- Review special considerations in doing research with human subjects
Materials

- List of definitions
- Reference materials
- Regulations and guidance
- Forms, templates and checklists
Terminology and Regulatory Definitions

- **Protocol**: connotes a research study. Sometimes used to refer to a standard of practice.

- **Randomized**: treatment assigned by ‘luck of the draw’. Designed to eliminate bias.

- **Stratification**: separates out confounding factors *a priori*. Designed to lead to balanced numbers of subjects with each stratified clinical feature.

- **Blind**: treatment assignment is masked. Single-blind, the patient is blind. Double-blind, both the patient and investigator are blind. Triple-blind, the monitor is additionally blind. Maneuver is designed to eliminate bias in assessment of response or adverse event.

- **Open-label**: No blind is being used.
Terminology and Regulatory Definitions

- **Double-dummy**: When comparing two treatments that are unmatched, patients must take two treatments, one active and one placebo.
- **Placebo-controlled**: Inactive substance used as comparator.
- **Multi-centered**: Several, or many, centers involved in the trial. Most often used with drug manufacturer sponsored trials. Often involve multi-national studies as well.
- **Cross-over**: Subjects will be randomly assigned to start with one treatment, then switched over to the alternate (usually after a wash-out).
- **Pre-clinical**: Animal pharmacology and toxicology studies.
Terminology and Regulatory Definitions

- **Phase I**: Studies done in normal healthy volunteers or patients with disease, primarily to determine toxicity (safety).

- **Phase II**: Controlled clinical trials designed to demonstrate efficacy and relative safety. Normally, these are performed on closely monitored patients of limited number.

- **Phase III**: Expanded trials, performed after effectiveness has basically been established at least to a certain degree. Intended to gather additional evidence of effectiveness for specific indications, and more precise definition of drug-related adverse effects.

- **Phase IV**: Post marketing studies.
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.
Ethical Foundations of Human Subjects Research

- Nuremberg Code (1949)
- Belmont Report (1979)
- Declaration of Helsinki (1964, updated 2000)
National Research Act

- Enacted in 1974
- Established National Commission for Protection of Human Subjects of Biomedical and Behavioral Research
  - Belmont Report
- Established the IRB system for regulating research
INSTITUTIONAL REVIEW BOARD

- Responsible for protecting the rights and welfare of human subjects participating in research studies
- Ensure research is conducted in accordance with accepted ethical standards
What governs/drives the IRB?

- Ethical Principles
- Federal Law
- Federal Agencies and Their Regulations, Directives, Policies, and Guidance (FDA, DHHS, OHRP)
- Yale University Assurance to DHHS (FWA)
- Connecticut (State) Law & Regulations
- Good Clinical Practice (GCP) (ICH)
- University and HIC Policy
Belmont Report Ethical Principles

- Respect for Persons
- Beneficence
- Justice

- Contains the ethical principles upon which the U.S. Federal regulations for protection of human subjects are based
Respect for Persons

- Individuals should be treated as an autonomous agent
- Those with diminished autonomy should be protected
- Voluntary participation
Respect for persons

- Subjects have the right to choose what will or will not happen to them (Autonomy)
  - Informed Consent (a process/dialogue - not a single document)
    - Information
    - Disclosure (the procedure(s), purposes, risks and anticipated benefits, where therapy is involved – alternatives, etc.)
    - Comprehension
      - Manner & context (organized, enough time to review, etc.)
      - Vulnerable populations (special populations)
    - Voluntariness
      - free of coercion & undue influence
  - Those with diminished autonomy should be protected
Capacity to consent

- **Standard for Assessing Capacity to Consent** *
  - Ability to evidence a choice (communicate yes or no)
  - Ability to understand relevant information (procedures and rights)
  - Ability to appreciate the situation and its likely consequences (what he/she will experience and likely outcome)
  - Ability to manipulate information rationally (focus on process not the decision – is the decision consistent with the religious, moral and other belief's) of the subjects?)

* R. Amdur, M.D., ed. 2002: IRB Management and Function, Research Involving Adults with Decisional Impairment Chapter 9.4
Beneficence

- Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being.

- Two general rules
  - Do not harm
  - Maximize possible benefits/minimize possible harms

- Are the risks presented justified?
Beneficence

- Initial analysis as part of approval of the proposed protocol
- Ongoing monitoring of risks and benefits throughout the study (via data and safety monitoring plan)
Justice

- The Belmont Report tells us, “An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly…”
- Ethical Obligation: fair sharing of burdens and benefits
- Requirement: Equitable selection of research subjects; fairness in inclusion and exclusion criteria
Justice

- Does the research involve individuals who are unlikely to benefit from the results of the research?

- Who is likely to benefit? What connection do they have to the research subjects?
Regulations and Guidance

- 45CFR46, “The Common Rule” DHHS
- 21CFR50, 56, FDA
- Federal Wide Assurance (FWA)
- Office of Human Research Protections (OHRP)
- State of Connecticut (statutes, regulations and case law)
- International Conference on Harmonization (ICH)
Federal Regulations and Guidance

- Apply to research that is conducted by or supported by (funded by) the Federal government (NIH)
- Investigational drugs and devices under the jurisdiction of FDA
- Institutions (or individuals) engaged in research must file an assurance that they will follow recognized ethical principles and Federal regulations (Federal Wide Assurance, FWA)
The Office for Human Research Protections (OHRP) provides leadership and oversight on all matters related to the protection of human subjects participating in research conducted or supported by the U.S. Department of Health and Human Services (HHS). OHRP helps ensure that such research is carried out in accordance with the highest ethical standards and in an environment where all who are involved in the conduct or oversight of human subjects research understand their primary responsibility for protecting the rights, welfare, and well-being of subjects.
OHRP

- establishes criteria for and approves assurances of compliance for the protection of human subjects with institutions engaged in HHS-conducted or -supported human subject research,
- provides clarification and guidance on involving humans in research,
- develops and implements educational programs and resource materials, and
- promotes the development of approaches to enhance human subject protections
Connecticut law

- Age of majority
- Emancipated minors
- Reporting child and elder abuse
- Reporting certain communicable diseases (HIV, Hepatitis)
- Conservators of mentally retarded cannot give permission for participation in research
- Law silent on role of proxy consent for research
ICH

• The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.
ICH

- The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.
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.
- Deputy Director, Kathleen Uscinski, CIP, MBA
- Compliance Manager: Melody J. Sacatos CIP
- Committee Manager: Cathleen Montano, J.D.
- Expedited Review Manager: Brandy Henriques, CIP
- Coordinators: Diane Richitelli, CIP, Adamina Roman, MS
- Administrative Staff: Constance Costa, Lori Filipelli, 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
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 (selected by the coordinator)
- Re-Approvals
  - Reviewer (selected by the coordinator)
- Amendments
  - Reviewer (selected by the 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 – 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
- Will discuss under special considerations
- 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: AE reporting

- **Definitions:**
- **Adverse Event:** An undesirable and unintended, although not necessarily unexpected, result of therapy or other intervention.
- **Unanticipated:** An event is “unanticipated” when it was unforeseeable at the time of its occurrence.
- **Related:** An event is “related” if it is likely to have been caused by the research procedures.
- **Serious Adverse Event:** Any adverse event that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
Special Considerations in Human Subjects Research: AE reporting

- The HIC requires reporting ONLY for serious AND unanticipated AND related events in a timely manner (within 48 hours).
- This will require that each Data and Safety Monitoring Plan contain a protocol specific definition and examples of ‘serious’ and ‘related’ events that will be reported. The HIC should receive all possible, probable and definitely related events. This decision should be based on the risk level of the protocol as well as what is already known about the study intervention. Local principal investigators should assess any reports submitted in terms of need for change to the procedures or consent form. This is accomplished via HIC Form 6A for local events, and HIC Form 6B for off-site events.
The HIC requires that the protocol’s Data and Safety Monitoring Plan specify whether a Data and Safety Monitoring Board (DSMB) or Committee (DSMC) exists. If one exists, it should specify that it is the responsibility of that board to review comprehensive, cumulative, unblinded safety reports and employ stopping rules if there is evidence of differential effects in either risk or benefit. Further, recommendations of the DSMB will be submitted to the HIC upon receipt, and also upon submission of the protocol for reapproval. In approving the plan, the HIC must ensure that such a DSMB is free of conflict of interest, properly constituted, and that the stopping rules are appropriate.
Special Considerations in Human Subjects Research: AE reporting

- The HIC does not require reporting of all adverse events, especially those that are not serious, and those that are anticipated. When a DSMB is in place, tallying up numbers of adverse events is not necessary or helpful.
Special considerations in human subjects research: Major Protocol violations

- The deviation has harmed or posed a significant risk of substantive harm to the individual research subject and increased the risk/benefit ratio, OR
- The deviation has compromised the scientific integrity of the data collected for the study, OR
- There is evidence of willful or knowing misconduct on the part of the investigator(s) or study staff, OR
- The investigator(s) or study staff demonstrated other serious or continuing noncompliance with federal, state or local research regulations.
Special considerations in human subjects research: Protocol violations

- Investigators are required to report major protocol deviations that occur only at Yale’s research site(s) to the HIC within five (5) working days of their occurrence or within five (5) days of the investigator becoming aware of their occurrence. Investigators are also required to report results of audits or inspections conducted by sponsors or other external entities such as the Food and Drug Administration (FDA), which involve a major protocol violation as defined above.
Special considerations in human subjects research: Conflict of interest

- Ensure compliance with University’s COI Policy
- HIC reviews protocol-specific instances of potential COI
- HIC may find no issue, an issue to be managed, or an issue that does not allow the research to proceed as planned
- Management may include disclosure in the consent process, use of a consent monitor, or naming a different PI
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: Emergency use

- Prior HIC approval not required; investigator must notify HIC within 5 days
- Written informed consent is required unless waived
- HIC acknowledgement letter may be requested by sponsor
- HIC website has sample Notification Letter, and ‘generic’ consent form that can be used
Special considerations in human subjects research: Treatment INDs and parallel track

- Both require prospective HIC review and approval
- Written informed consent required
- In urgent cases, the protocol and consent form may be scheduled for ‘walk-through’ one of the committees by the Chair.
Special considerations in human subjects research: NCI Group C and Special Exceptions

- For Group C designated drugs, FDA has generally granted a waiver from the IRB review requirements. *HIC will allow this waiver if time does not allow for full committee review.*

- The usage of a Group C drug is described in its accompanying "Guideline Protocol" document. The Guideline Protocol contains an FDA-approved informed consent document which must be used if there has been no HIC review.
Special considerations in human subjects research: NCI Group C and Special Exceptions

- The Special Exception mechanism is the functional equivalent of a compassionate IND but it differs from it in that the investigator may obtain investigational agents directly from CTEP, instead of having to obtain an IND from FDA. Agents distributed under this mechanism are investigational and are subject to FDA regulation and CTEP Policy. Protocols utilizing the Special Exception mechanism either must be reviewed by the full committee, or meet the requirements for expedited review.

- Reporting of adverse events is required for all NCI Special Exception and Group C protocols
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...)

Special considerations in human subjects research: HIC and the YCC QUACS

- Serious issues identified by audits must be reported to HIC
- Corrective action plans are an important part of any report
- HIC and QUACS will coordinate actions and reporting to institutional officials, OHRP, and FDA
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.