PURPOSE AND FUNCTION OF IRBS

SUCCESES AND CHALLENGES

Barbara I. Karp, M.D.
Chair, CNS IRB, NIH
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History of Institutional Review Boards

- 1966: NIH Policy for the Protection of Human Subjects
  - Established IRBs as a component of the subject protection system

- 1974: DHEW- implemented NIH policy as regulations

  ----> **Belmont Report** published in 1978
1981: 45CFR46 codified the DHHS regulations

1991: 45CFR46 revised and subpart A adopted by 15 Federal departments and agencies as the “Common Rule”

FDA formulates its own parallel policies: 21CFR50, 21CFR56
  • 21CFR56 relates specifically to IRBs
45CFR46

Defines RESEARCH

A systematic investigation designed to develop or contribute to generalizable knowledge

Defines HUMAN SUBJECT

Living individual about whom an investigator conducting research obtains data through intervention or interaction or identifiable private information

Defines IRB

IRB means an Institutional Review Board established in accord with and for the purposes expressed in this policy
45CFR46

Defines minimal membership

At least 5 members
Neither all men nor all women
Qualified via experience and expertise
Diversity of race, gender, cultural background
Sensitive to community interests
Knowledgeable about subject matter of research
Knowledgeable about specific populations
At least one member whose primary concern is scientific
At least one member whose primary concern is not scientific
At least one member not affiliated with the institution
45CFR46

Defines functions and operations

Initial review
Review of modifications (amendments)
Continuing review no less than annually

Review of informed consent documents and process
45CFR46: Criteria for approval

1. Risks to subjects are minimized
   a. Using procedures consistent with sound scientific design
   b. Using procedures already planned for diagnosis or treatment

2. Risks are reasonable in relation to anticipated benefit and importance of the knowledge reasonably expected
   a. Can only consider the risks and benefit from the research itself, not from those subject would be exposed to anyway
   b. IRB should not consider long-range effects
45 CFR 46: Criteria for approval

3. Selection of subjects is equitable
   a. PL103-43 requires gender/minority subanalyses for phase 3 clinical trials
   b. Exceptions may be approved based on scientific or safety concerns

4. Informed consent is obtained from subject or LAR
   a. Informed consent may be waived if certain conditions are met

5. Informed consent is properly documented
   a. Written informed consent may be waived if certain conditions are met

6. Research plan has provisions for monitoring

7. Research plan has provisions for protecting privacy and confidentiality
Additional provisions for

1. Pregnant women and fetuses (subpart B)
2. Prisoners (subpart C)
3. Children (subpart D)
IRB FUNCTION

IRBs operate under institutional FWA and must be registered with OHRP

Reviews:

- new protocols
- continuing review
- amendments
- adverse event reports
- protocol deviations/ violations
- terminations
- advertisements
- reports of misconduct
What happens at meetings

- All IRB members receive all submissions in advance and are expected to have read all materials.

- Each submission is discussed. Some IRBs use a “primary reviewer” to present to the IRB.

- PI or representative may attend to answer questions from the IRB.

- At NIH, protocol review standards must be addressed at initial review.
What happens at meetings

• The Chair conducts the meeting from a preset agenda.

• Meetings and votes require a quorum of members (50%+1) and the presence of a lay member.

• Each item is open for discussion. Observers leave the room for voting.

• A motion is made for IRB action. Only active IRB members or their duly designated alternates vote. The IRB Chair may choose not to vote except to break a tie.

• IRB decisions are conveyed to the PI in writing.
IRB Actions

Approve without stipulation

Approve with stipulations

Stipulated revisions require only concurrence on the part of the investigators. Review of response to stipulations delegated to Primary Reviewer and IRB Chair.

Defer approval

Substantive changes are stipulated. Review of response to stipulations comes back to entire Board. Approval will be granted if stipulations are met.

Table

Substantial revision needed (beyond stipulations and concurrence). IRB provides recommendations for revision. IRB does a complete re-review of the revised documents.

Disapprove

Institutional administration cannot overrule IRB disapproval. At NIH, cannot resubmit to a different IRB; can appeal to same IRB.
Expedited Review

Initial review, CRs and amendments that meet certain criteria may be eligible for “expedited review.” Expedited review is conducted by the IRB Chair or designees of the Chair who exercise all of the authorities of the Board, except that disapproval requires full IRB review.

• Expedited review is not necessarily faster than full Board review

• All Protocol and Consent requirements apply

• All PI requirements apply
Expedited Review

Research activities that **present no more than minimal risk to human subjects, and involve only procedures listed in one or more of the categories identified below**, may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed below should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review procedure when the specific circumstances of the proposed research involve no more than minimal risk. The categories apply regardless of the age of subjects, except as noted.

The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects’ financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal. In addition, it may not be used for classified research involving human subjects. Standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review – expedited or convened – utilized by the IRB.
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Protocol Stages: IRB role

Preparation of the protocol
Concept
Design
Drafting
Approval
Recruitment
Screening
Enrollment
Conduct of study
Study procedures
Monitoring
Data collection
Study completion
Data analysis
Reports/publications
Archiving
Study Procedures

To FDA
To DSMB
To IRB
To sponsor

Data Collection

Source documents
Medical Records
Investigator Records

Monitoring

Reporting

AEs/ SAEs
Compliance
Deviations
Violations
Study Ends

- Enrollment complete
  - Endpoint reached
    - Stop rule invoked
  - Other

Data Set Closed

- Archive
- Export
- Analyze

Report/publication

Terminate Protocol

Approved by IRB
IRB SUCCESSES

Institutional IRBs well-utilized

Commercial/ non-institutional based IRBs appropriate for some research

Few reports of avoidable harm

Hold investigators responsible for protecting subjects

Involves community in research review
IRB CHALLENGES

Lack of outcome measures for IRB function

No validated methodology for evaluating IRBs

- How do we know if an IRB is functioning well and doing its job
- Cannot determine the number of subjects NOT harmed because of IRB review

No standard criteria for selecting/evaluating IRB Chairs and members
IRB CHALLENGES

Lack of uniformity in the review process

No standard way of reviewing submissions

No standard way of identifying risks

No standard way of determining “minimal risk” or “minor increase over minimal risk”
IRB CHALLENGES

1. IRB review and scientific review

2. Monitoring: IRBs and DMSBs

3. Mission creep

4. Maintaining efficiency in face of increasing regulation

5. Interpreting and providing protections for emerging technologies

6. Lack of resources; lack of IRB professional standards and trained staff
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IRB CHALLENGES: “science”

Claim: IRBs inappropriately review the “science” of the study

• IRBs are not charged with reviewing the science, just ethics
• IRBs are not capable of understanding/reviewing the science

BUT....

Poorly designed studies that cannot provide valid data are unethical (all risk without benefit even from generalizable knowledge)

Common Rule requires that IRBs have the expertise to understand the study, including scientific and medical aspects

Scientific reviews vary in quality; IRB may need to review scientific aspects of the study
IRB CHALLENGES “science”

Case examples

1. Study of a new medication for cognitive function in schizophrenia is designed with an 8 week drug “wash-out” phase. IRB determines that wash-out is not critical for study design and greatly increases risks to subjects.

2. Study of an intrathecal infusion of elemental drug to treat fatal disease in neonates. Animal studies not completed on uptake of element into the brain with intrathecal administration or on its safety. PI argues that the animal models are suboptimal and are therefore not needed.
IRB CHALLENGES “science”

Case examples

3. Study of effect of DRUG A on Parkinson's disease. DRUG A causes liver damage in 10% of subjects. DRUG B works by same mechanism but does not cause liver damage. IRB stipulates study should use DRUG B instead of DRUG A.

4. Phase 1 dose-finding study of new drug in small cohort. PI proposes a placebo arm to get preliminary data on efficacy and safety. 2 infusions (drug/placebo) require prolonging hospitalization and PICC line insertion. Study is not powered to get valid data on safety or efficacy. IRB determines risk of placebo phase outweighs benefit and requires that placebo infusion not be done.
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IRB CHALLENGES: Monitoring

IRBs and DMSBs: Who’s minding the store?

Data and Safety Monitoring Boards
1998 NIH Policy for Data and Safety Monitoring

• Should be independent of investigators
• Have the scientific expertise to interpret data and ensure patient safety: clinical trial experts, statisticians, ethicists, clinicians, lay persons
• Maintain confidentiality
IRB CHALLENGES: Monitoring

Data and Safety Monitoring Boards
A group of independent experts that reviews the ongoing conduct of a clinical trial to ensure continuing patient safety as well as the validity and scientific merit of the trial

Problems:
No accepted standards for DSMB structure or function
No clear reporting/responsibility pathway
? Independent authority
? Advisory to PI
? Advisory to IRB- if conflict, who prevails?
IRB CHALLENGES

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“Simultaneous overregulation and underprotection”
IRB CHALLENGES: Mission Creep

Tasks that are falling on IRBs

1. Review of “studies” that aren’t research (interviews, journalism, secondary use of public data)
2. Focused on documentation and compliance rather than subject protections, exacerbated by IRB accreditation
3. Protocol editing/ consent writing
4. Training investigators on how to write and conduct research
5. Institute administration
   a) Establishing guidelines on the conduct of research
   b) Establishing policies
   c) Risk management/ institutional liability
   d) Conflict-of-interest management
6. Assuring that non-IRB related monitoring and reporting are completed (e.g. FDAA)
IRB CHALLENGES: Mission Creep

Examples from the Intramural Program

1. NIH travel policy
2. NIH COI policy
3. NIH compensation policy
4. NIH policy on clinical MRIs for subjects undergoing research MRI
IRB CHALLENGES

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IRB CHALLENGES: increasing regulation

1. AAHRPP accreditation- over-emphasizes written policies and documentation

2. FDA- literal definition of annual review as 364 days with minimal flexibility

3. OHRP Subpart E: staffing and resources

4. Conflicting regulations (eg AE/Unanticipated Problem reporting)

5. Independence
IRB CHALLENGES

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IRB CHALLENGES: new science, new society

1. DNA/genetics studies/genome and exome-wide analyses
2. Immortal cell lines/derivatives
3. Induced pluripotential stem cells
4. Banking/future use- samples and data
5. The Internet and research: Facebook, Google and on-line research/on-line consent
6. Mental/psychiatric/physical enhancement
7. Lie detection and other implications of science for criminal prosecution
8. Implications of research for broader community
9. Increasing international and collaborative research
10. Centralized IRB review
IRB CHALLENGES: new science, new society

1. Privacy and confidentiality- especially with multisite studies, use of repositories, Internet communication
2. Autonomy/ Control of personal data and samples
   a. Limiting potential uses
   b. Obtaining results of use
3. Compensation- right to payment for commercial development
4. Adverse outcome from research findings; returning results of unknown significance to participants
5. Societal/ subpopulations concerns related to data and use
IRB CHALLENGES

1. IRB review and scientific review

2. Monitoring: IRBs and DMSBs

3. Mission creep

4. Maintaining efficiency in face of increasing regulation

5. Interpreting and providing protections for emerging technologies

6. Lack of resources; lack of IRB professionals
IRB CHALLENGES: IRB staff/members

1. Chair often a clinical researcher with little HRP expertise

2. Staff are often re-assigned clerical staff rather than IRB professionals (e.g. CIPs)

3. Members often represent special interests and lack adequate preparation and training

4. Staffing often inadequate to volume of studies

5. Space, facilities and budgets often inadequate

6. Costs difficult to determine. IRBs often lack dedicated funding/ budget
IRB CHALLENGES.....SOLUTIONS???

1. IRB review and scientific review - Standards for scientific review, similar to journal peer-review. Standards for IRB review, criteria for how to evaluate IRBs

2. Monitoring: IRBs and DMSBs – Clear delineation of monitoring responsibilities and reporting pathways

3. Mission creep – Provide institutional resources to handle processes that are not related to the IRB.
4. Maintaining efficiency in face of increasing regulation – Regulatory agencies should work towards common policies, rather than redundant and conflicting policies. Revise/abandon outdated policies. Assure that regulations relate directly to the mission.

IRB CHALLENGES....SOLUTIONS???

6. Lack of resources; lack of IRB professionals – Institution should assure adequate resources and training for IRB professionals.
QUESTIONS

ANSWERS