PURPOSE AND FUNCTION OF IRBS

SUCCESSES AND CHALLENGES

Barbara I. Karp, M.D.
Chair, CNS IRB, NIH
October 3, 2012

National Institutes of Health
The Nation's Medical Research Agency

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

- 1974: National Research Act creates National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research ----> **Belmont Report** published in 1978

History of Institutional Review Boards

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**

45CFR46: 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**

45CFR46: Criteria for approval

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**

IRB

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

IRB

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.

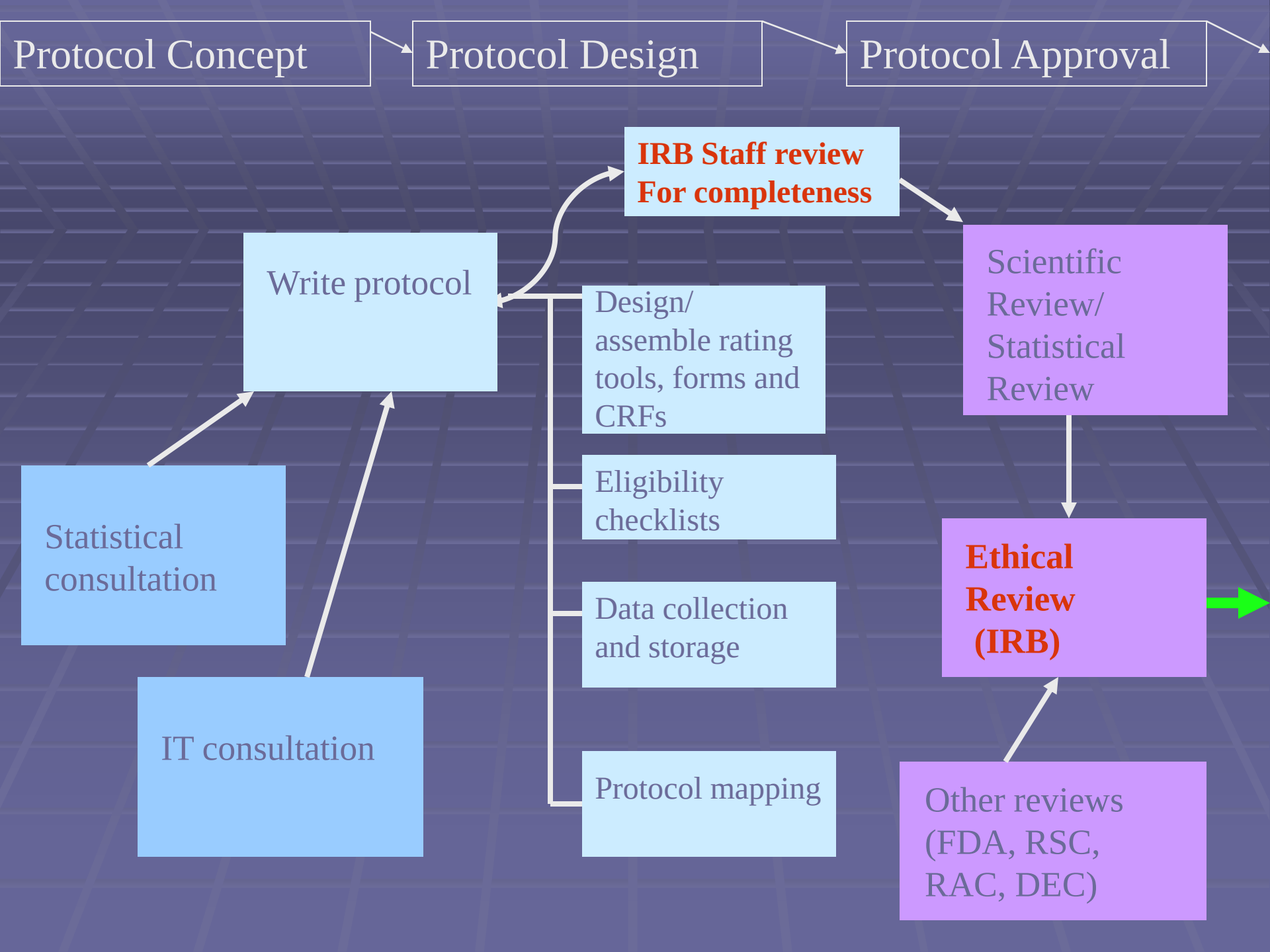
Expedited Review

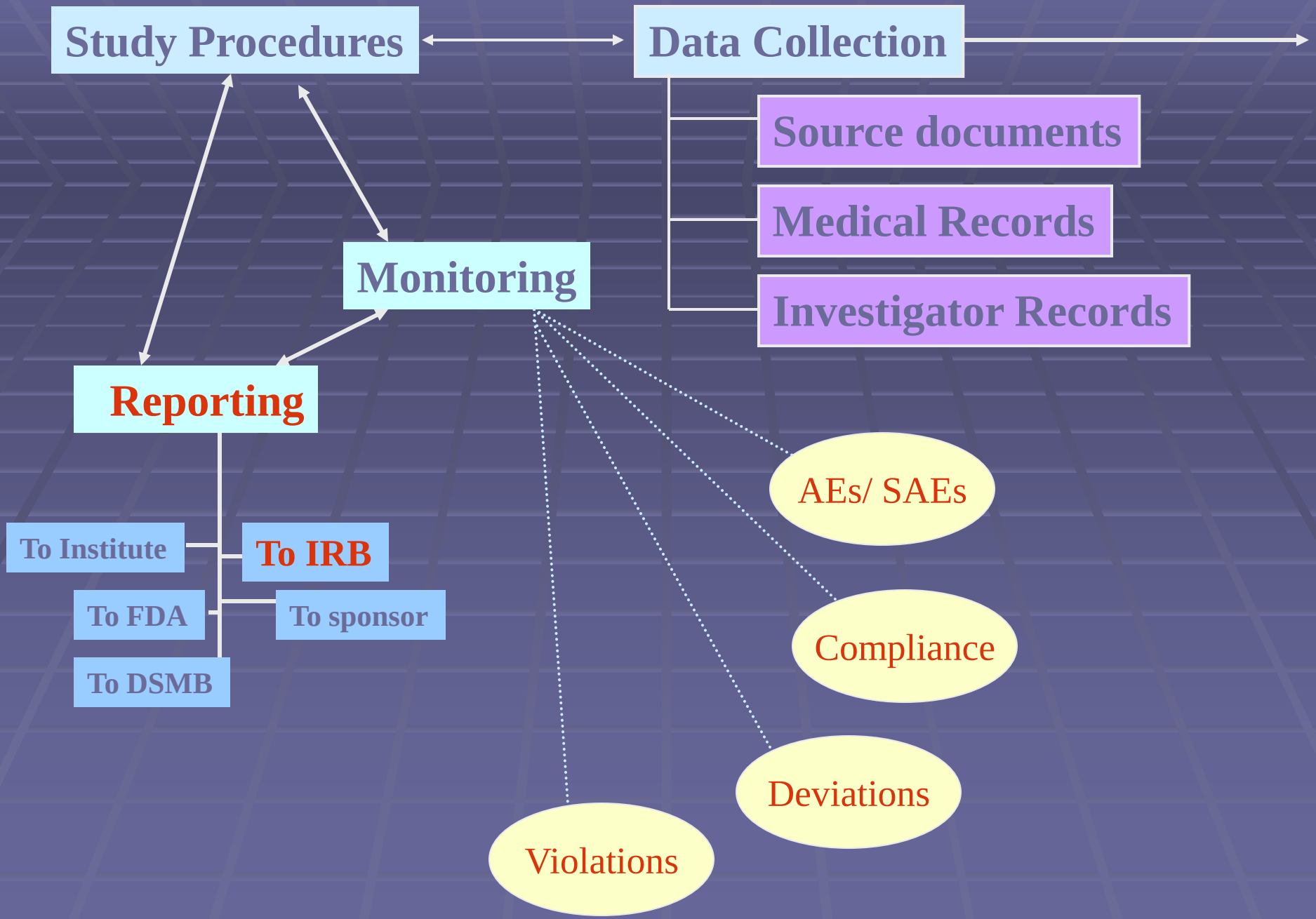
Research activities that **present no more than minimal risk to human subjects, and involve only procedures listed in one or more of the categories identified below,** may be reviewed by the IRB through the expedited review procedure authorized by 45 CFR 46.110 and 21 CFR 56.110. The activities listed 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.

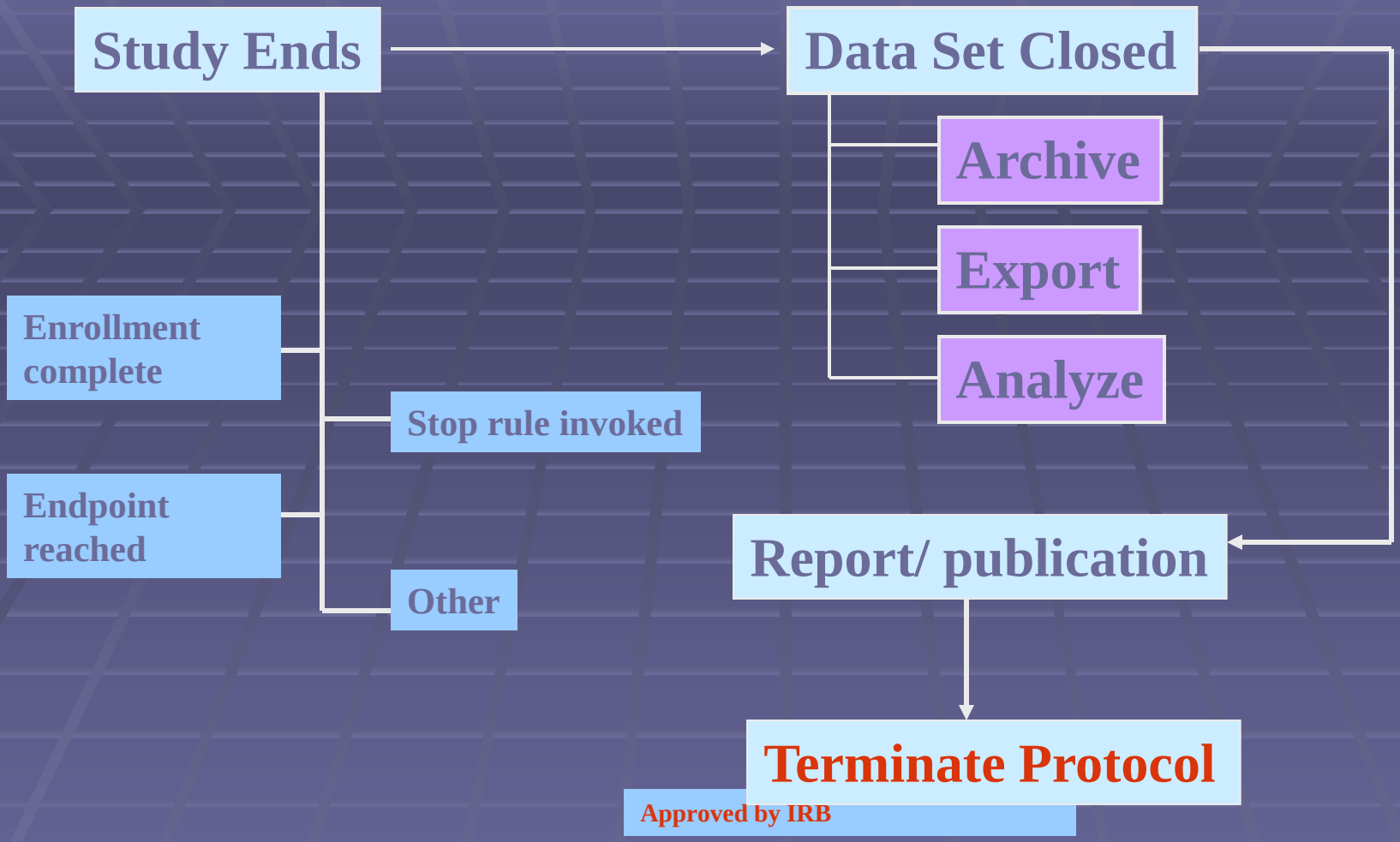
The expedited review procedure may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable 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.

Protocol Stages: IRB role

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


Protocol Concept
Protocol Design
Protocol Approval
IRB Staff review
For completeness
Write protocol
Design/
assemble rating
tools, forms and
CRFs
Eligibility
checklists
Data collection
and storage
Protocol mapping
Scientific
Review/
Statistical
Review
Ethical
Review
(IRB)
Other reviews
(FDA, RSC,
RAC, DEC)
Statistical
consultation
IT consultation


Study Procedures
Data Collection
Source documents
Medical Records
Investigator Records
Monitoring
Reporting
To Institute
To IRB
To FDA
To sponsor
To DSMB
AEs/ SAEs
Compliance
Deviations
Violations


Study Ends
Data Set Closed
Archive
Export
Analyze
Enrollment complete
Stop rule invoked
Endpoint reached
Other
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**

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**

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.**

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: 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

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: Mission Creep

Mission Creep in the IRB World

The authors are all at the University of Illinois Urbana-Champaign and participated in the Center for Advanced Study Steering Committee to Study Human Research Protections.

C. K. Gunsalus, Edward M. Bruner, Nicholas C. Burbules, Leon Dash, Matthew Finkin, Joseph P. Goldberg, William T. Greenough, Gregory A. Miller, and Michael G. Pratt.

THE SYSTEM IN THE UNITED STATES FOR PROTECTING HUMAN PARTICIPANTS IN RESEARCH engages the earnest efforts of thousands of scientists, community volunteers, and administrators. Through untold hours of service on Institutional Review Boards (IRBs), they watch over the safety of human research subjects. Unfortunately, much of that effort is increasingly misdirected as the system succumbs to "mission creep" that could compromise its central goals. Our IRB system is endangered by excessive paperwork and expanding obligations to oversee work that poses little risk to subjects. The result is that we have simultaneous overregulation and underprotection.

IRBs were established after the 1979 Belmont Report from the Department of Health, Education, and Welfare, with the goal of protecting human subjects involved in potentially risky medical and behavioral research. But IRBs' burdens have grown to include studies involving interviews, journalism, secondary use of public-use data, and similar activities that others conduct regularly without oversight. Most of these activities involve minimal risks—surely less than those faced during a standard physical or psychological examination, the metric for everyday risk in the federal regulations. And IRBs are pressured to review an expanding range of issues from research design and conflicts of interest to patient privacy. These are beyond the scope of research protection and are best left to others.

The IRB system is being overwhelmed by a focus on procedures and documentation at the expense of thoughtful consideration of the difficult ethical questions surrounding the welfare of human subjects, especially as complex clinical trials burgeon. Their work is afflicted by unclear definitions of terms such as "risk," "harm," and "research." Because ethical behavior is difficult to measure, many IRBs rely on stylized documentation over substantive review, out of concern that one case in a thousand could slip through and generate bad publicity or penalties, or potentially shut down research. The result is that many protocols receive exaggerated review, and the paper piles up. Society loses as potentially productive research is discouraged or self-censored.

Ironically, this obsession with paperwork and mechanical monitoring may undermine protection of human subjects. IRB members spend too much time editing documents, marking typos, and asking for more details.

"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

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: 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

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: 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.

IRB CHALLENGES….SOLUTIONS???

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

5. Interpreting and providing protections for emerging technologies – Federal-wide standards for privacy and confidentiality. Guidance on repositories, genetic testing, IPS cells, return of results, additional use of data/samples

IRB CHALLENGES….SOLUTIONS???

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

QUESTIONS????

ANSWERS ????