Protocol Development, Review, and Approval Process

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Planning a Clinical Trial

- Formulate the Research Question
- Develop the Study Design
- Define the Study Population
- Select the Measurement Tools/Endpoints
- Determine Sample Size and Statistical Analysis
- Data Collection and Storage

Formulate the Research Question

- Define Objective(s) clearly and precisely
- Objective(s) need to be tied to measurable study endpoints
- Primary objective of the study must be identified
- May have several secondary objectives

Characteristics of a Good Research Question – "FINER"[1]

- Feasible
  - Adequate number of subjects
  - Adequate technical expertise
  - Affordable in time and money
  - Manageable in scope
- Interesting
- Novel
  - Confirms or refutes previous findings
  - Extends previous findings
  - Provides new findings

- Ethical
- Relevant
  - To scientific knowledge
  - To clinical and health policy
  - To future research directions

[1] *Hulley, S.,B., Cummings, S.R., Browner, W.S., Grady, D., Newman, T.B. (2007). Designing Clinical Research (2nd Ed.), Philadelphia: Lippincott Williams & Wilkins.*

Select the Study Design

Selection of the study design is based on:

- study question
- ethical considerations
- resources

Study Subject Selection

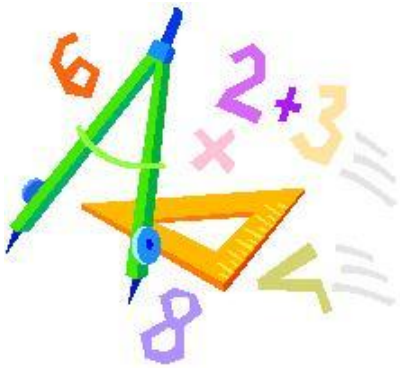
- Subjects who may benefit
- Subjects who may be at greater risk
- Subject's ability to comply
- Subject's concurrent conditions
- Inclusion criteria
- Exclusion criteria

Measurement Tools/Endpoints

- Toxicity
- Response
- Survival
- QOL/Patient Reported Outcomes (PRO)
- Biological Endpoints and Surrogate Markers

Determine Sample Size

- Get statistician involved early!!
- Estimate the appropriate number of subjects for a given study design
- Test the hypothesis
- How to handle dropouts/withdrawals?
- For interventional studies:
  - How large a difference between treatment groups is medically important
  - Include enough participants to get a statistically significant results



Determine Statistical Analysis

- Analysis plan appropriate for objectives and design
- How endpoints will be measured
- Statistical methods to be used
- How will common problems be addressed
- Management of safety data
  - DSMB?

Data Collection & Storage

- Identify critical data elements to be collected
- Develop case report forms
- Safe and secure mechanism for data storage
- Anticipate audits of clinical data
- Length of time for storage
  - Know FDA regulations
  - Know institutional policies as appropriate
    - NIH Manual Chapter 1743 “Keeping & Destroying Records

THE PROTOCOL

Clinical Research Protocol

A written, detailed action plan that:

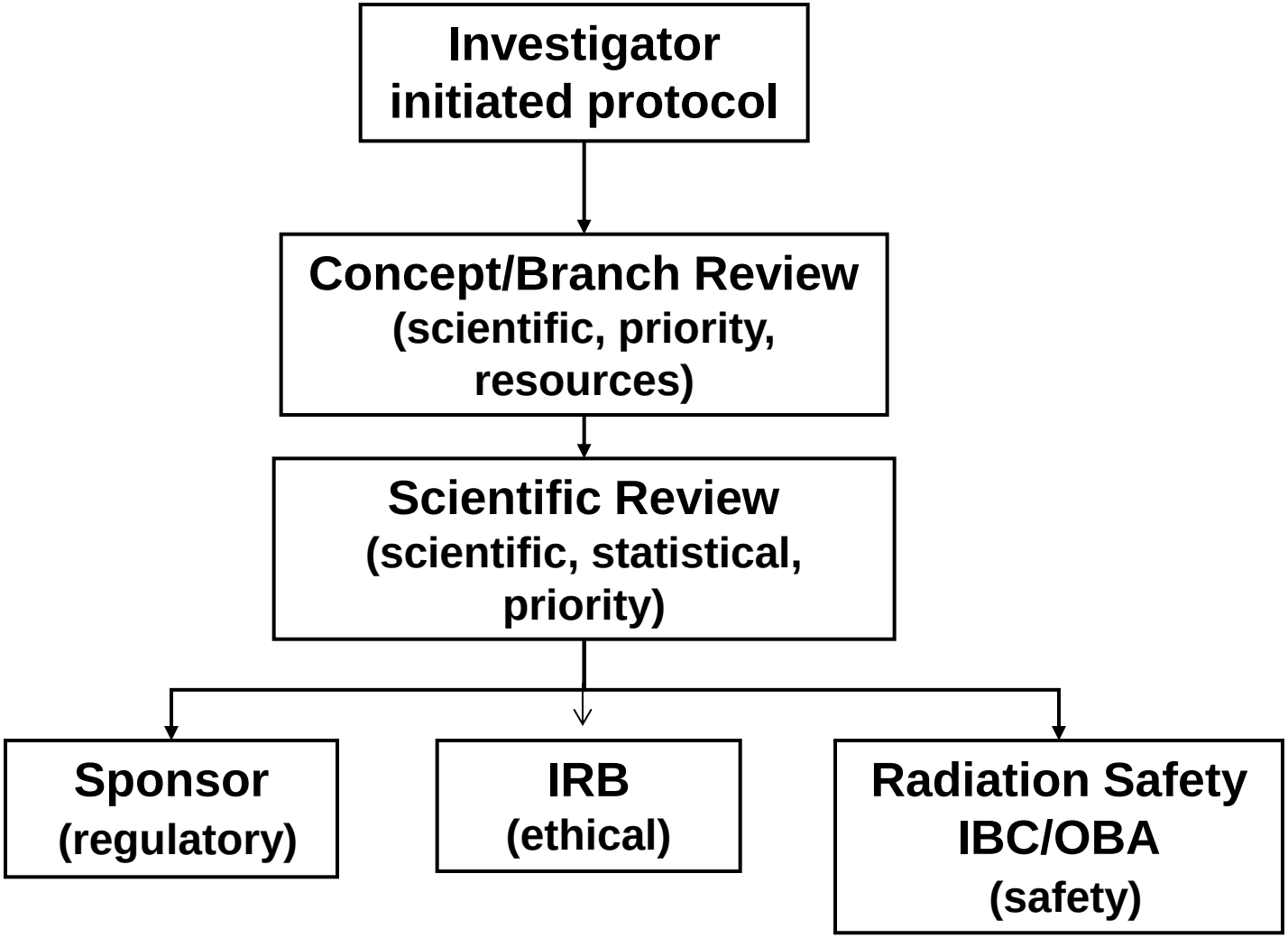
- Provides background about the trial
- Specifies trial objectives
- Describes trial's design and organization
- **Ensures that trial procedures are consistently carried out**

NOTE: Each IRB or Sponsor will have their own Protocol template.

Required Protocol Sections (SOP #8)

- Title page*
- Précis
- Table of contents
- Background
- Study Objectives
- Study design and methods
- Inclusion & Exclusion criteria
- Clinical and laboratory methods
- Collection and storage of human specimens or data
- Statistical analysis
- Human subjects protection
- Privacy and confidentiality
- Study agents/interventions
- Reporting requirements for UPS and AEs
- Data and safety monitoring plan
- Data/record management
- Compensation
- References
- Appendices

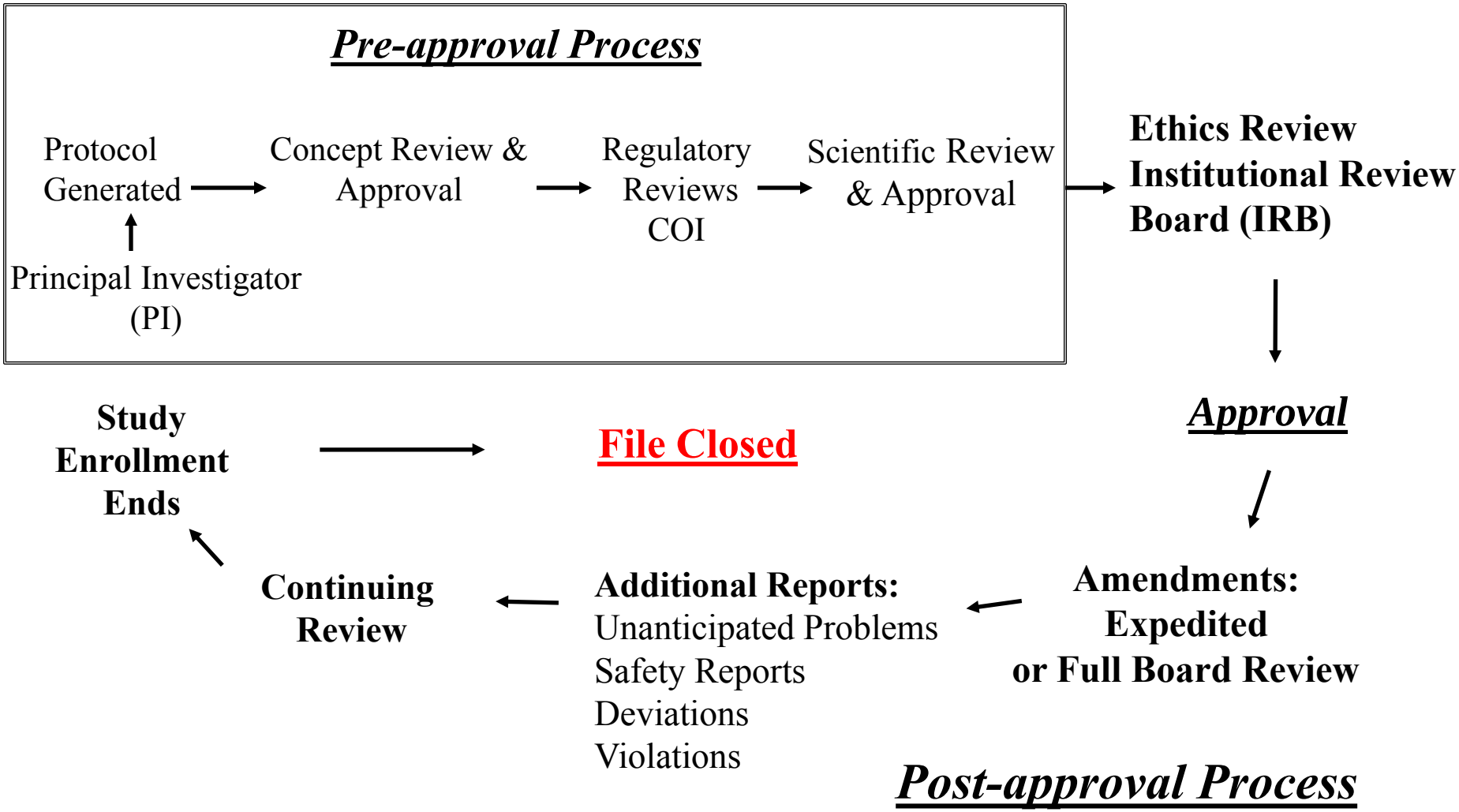
Protocol Development at the NIH IRP



Protocol Management Systems at NIH

- 2 web-based information management systems:
  - Integrated Research Information System (iRIS)
  - Protocol Tracking and Management System (PTMS)

Protocol Life Cycle



Branch/Concept Review

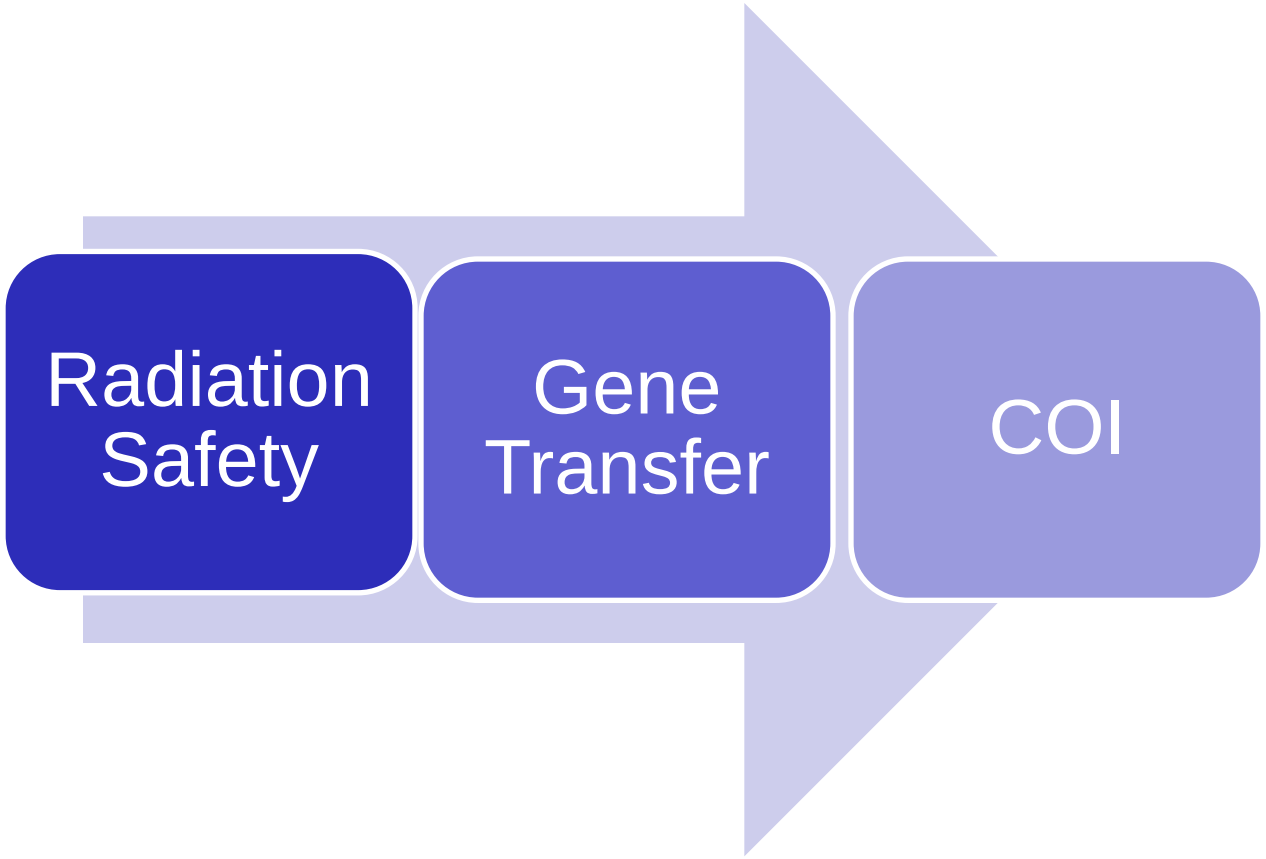
- Does it fit well within the research portfolio of the IC?
- Should it be given priority?
- Can it be accomplished with the proposed staff and resources of the Clinical Center?
- Does the IC have appropriate funds to support the study?

Scientific Priority + Resources

Scientific Review

- Institute or Branch Level Review
- Primary focus is science, not safety
  - Are the objectives of the study scientifically founded?
  - Are the design and methods correct?
  - Is this appropriate use of our resources?
  - (IRB is safety not science)
- First level of review before IRB review

Regulatory Considerations: Pre-IRB Approval



Radiation Safety

- NIH Radiation Safety Program
  - Ensure safe use of radioactive materials and all sources of ionizing radiation throughout NIH and NIH-occupied buildings
  - Radiation Safety Officer (RSO)
- Oversight by the Radiation Safety Committee (RSC)
- RSC and RSO report to NIH Director

Radiation Safety Committee

- Reviews protocols using ionizing radiation (x-rays, nuclear-medicine, PET) ***for research purposes***
- Approval by RSC is required before the initiation of IRB approved clinical research protocol
- RSC meets monthly
- Submit protocol using From NIH 88-23 (a) : Application for Authorization to use Radiation in Research involving Human Subjects
  - http://www.ors.od.nih.gov/sr/drs/rsc/Pages/index.aspx

Human Gene Transfer (HGT) Trials

- Research involving recombinant or synthetic nucleic acid molecules or DNA or RNA derived from recombinant synthetic nucleic acid molecules into human subjects to:
  - compensate for defective genes
  - produce a potentially therapeutic substance
  - trigger the immune system to fight disease

HGT Research Oversight

Federal

- NIH IC Program Staff
- NIH OBA
- OHRP
- FDA

Local & Non-Federal

- IBC
- IRB
- Investigators
- Sponsors

Institutional Biosafety Committee (IBC)

- Group of experts that provides local review, oversight, and approval of HGT research

- Follow *NIH Guidelines for Research Involving Recombinant DNA Molecules*

Responsibilities of an IBC…

- Examine experimental protocols that are submitted
- Evaluate the expertise of the Principal Investigator (PI) and staff to conduct the work
- Evaluate the potential dangers of the work
- Evaluate the biological containment plan and facilities per the NIH Guidelines

… Responsibilities of an IBC

- Determine whether additional expertise should be consulted
- Determine whether health surveillance of laboratory staff is necessary
- Request additional information from PI
- Approve or disapprove the protocol

NIH IBC

- Provides recommendations to NIH Director in matters pertaining to the control of hazards associated with the intramural use of microbiological agents, their vectors, and recombinant DNA
- Committee serves as an advisory body to the Division of Occupational Health and Safety (DOHS), Office of Research Services (ORS)
- PI-dashboard used for submissions
- http://www.ors.od.nih.gov/sr/dohs/SafetyResources/committees/Pages/inst_biosafety_committee.aspx

Office of Biotechnology Activities (OBA)

- NIH office promoting science, safety and ethics in biotechnology
- Establish and maintain the *NIH Guidelines for Research Involving Recombinant DNA Molecules* First published in 1976 - Evolved over time with increase scientific understanding & technological developments

http://oba.od.nih.gov/oba/index.html

NIH Guidelines: Appendix M

- Articulate principles for the safe and ethical conduct of HGT research to allow research to move forward safely and with public acceptance
- Requirements for Information Submission to NIH:
  - Protocol
  - Responses to questions about the scientific and safety-related dimensions of the gene transfer intervention
  - Issues pertinent to the informed consent process
  - Safety and Annual Reporting Requirements
- RAC Review Process

Recombinant DNA Advisory Committee (RAC)

- Federal advisory committee composed of national experts to provide advice and recommendations to the NIH Director regarding HGT research
- NOT an approval process

Summary of HGT Protocol Review Process

- Protocol submitted to OBA
- Sent to RAC Members
- RAC Members review and recommendations
  - May or may not be selected for full RAC review
- Written review sent to PI
- Written response to OBA
- Public discussion at RAC meeting
- OBA Letter

Timing of Protocol Review

- Final IBC approval cannot occur until RAC review is completed
- IRB review and approval can occur before or after RAC review
- FDA review and authorization of IND application can occur at any time

Post-Enrollment Reporting

- Within 20 days of enrollment of the first participant, PI must submit to OBA:
  - Response to RAC recommendations (if applicable)
  - Copy of final protocol
  - Copy of final IRB-approved informed consent
  - Copy of IRB approval
  - Copy of IBC approval
- Subsequently, PI must submit:
  - Protocol amendments
  - Serious adverse event reports
  - Annual reports
    - Due within 60 days after the one-year anniversary date of IND authorization and yearly until trial is completed

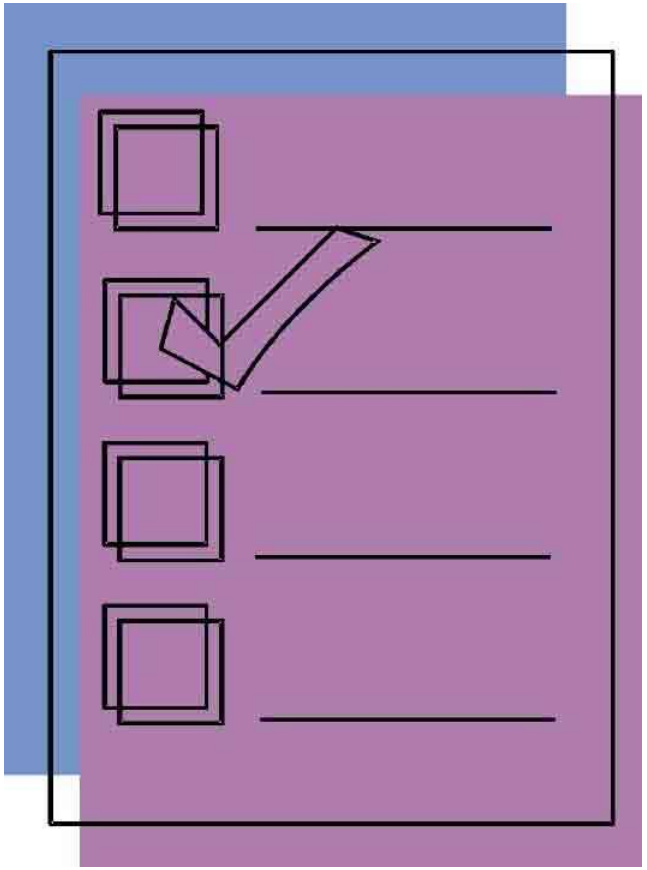
Conflict of Interests and Financial Disclosures

Federal regulations and Institutional policies require that investigators disclose any significant financial interests that may present an actual or potential conflict of interest in relationship to externally sponsored research prior to the initiation of a protocol/study

Financial Disclosure

- FDA Financial Disclosure by investigators – 21 CFR 54
  - Form 3454: certification
  - Form 3455: disclosure

- PLUS NIH requirements: Deputy Ethics Counselor's (DEC) Clearance



NIH COI…

- NIH Employees: NIH Ethics Office
  - Key Research Personnel: based on their role on the protocol not just their designation on the protocol
    - All individuals involved in recruiting and enrolling human subjects
    - Obtaining informed consent
    - Reviewing/reporting adverse events
    - Analyzing data
  - IRB members
  - DSMB members
- Non-NIH Employees: PI

…NIH COI

- Clearance of NIH Investigator Personal Financial Holdings by IC Ethics Office
- Submit for:
  - New Protocol
  - Continuing Review
  - Amendment (Investigator Added or Product Added or Changed)
- Assessing for conflicts or financial interests
- NIH Ethics Program
  - http://ethics.od.nih.gov/

Role of the IRB

- A committee charged with the review of human subject research
- Primary mandate is to protect and safeguard the rights and welfare of human subjects
  - Balance rights of individual subjects with development of knowledge to further society as a whole

IRB Assurances & Registration

- Agreement between the institutional official of a research entity and the DHHS
- Purpose:
  - establish binding agreement between institution and government that the institution agrees to comply with the Federal Regulations for the Protection of Human Subjects
- Registration of the IRB with DHHS

IRB Membership

- Minimum of 5 Members
  - 1 member whose primary concerns are in the scientific areas
  - 1 member whose primary concerns are in nonscientific areas
  - 1 member who is not affiliated with the institution
- Various backgrounds and professional competence to review specific research activities
- Diverse by race, gender, and cultural backgrounds and sensitivities to such issues as community attitudes

…IRB Membership

- Knowledgeable and experienced if working with vulnerable subjects
- No participation on a given project in which they or their family have a conflict of interest
- Invited experts in an area beyond or in addition their expertise to review a project and provide input for the Board's consideration
- OHRP YouTube video

  http://www.youtube.com/watch?v=GHtIbdLkSwU

NIH IRB SOP #2 Additional Requirements

- Scientific or professional staff member not affiliated with the IRB's Institute
- Member with expertise in statistics or an epidemiologist
- Member who is either a pharmacist or pharmacologist, **and**
- An ethicist or individual who has expertise in the ethics of human subjects protection
  - CC Department of Clinical Bioethics s

Membership Roster

Must be current

- First and Last Name
- Earned Degrees
- Phone Number
- E-mail Address
- Term Start Date
- Term End Date
- Scientific Status (scientist or non-scientist)
- Affiliation Status
- Area of Specialty
- Narrative Description of Area of Expertise
- IRB Officers (e.g. Chair, Vice-chair)
- Membership Status (e.g., primary or alternate)
  - Alternate Member(s) and who they can alternate for

IRB Meetings

- Regulations require a quorum
  - More than half the members present at the meeting
  - Example: 22 IRB members then you need 12 people need to be present
- Check your IRB website for meetings dates and due dates for submissions

IRB Meeting Minutes

Minutes must be in sufficient detail to show the actions undertaken by the IRB including:

- Meeting Attendance (quorum)
- Vote on the action
- Summary of the discussion
- Controverted issues and their resolution
- Majority of the members are present
- Conflicts of interests of members and their recusal
- Determinations of the IRB including conditions (stipulations) for approval

What Must Be Submitted For Review?

- New protocols
- Amendments to existing protocols
- Continuing reviews
- Adverse events
- Safety/Compliance Reports
- Deviations & Violations
- DEC Clearance – COIs
- Status changes

IRB Review

Types of Review

- Full Board Review
- Expedited
  - No greater than "minimal risk"
  - Chair or designee
- Exempt (HRPP review, no IRB review, SOP #)

Possible Outcomes

- Approve
- Approve with Stipulations
- Defer Approval
- Table
- Disapprove

Basic IRB Review Standards

- Research is sound and with no unnecessary risks
- Risks are reasonable in relation to anticipated benefit
- Subject selection is equitable
- Adequate safeguards for vulnerable populations
- Informed consent document & methods acceptable
- Subject safety is maximized
- Privacy and confidentiality considered
- Regulatory issues approved
- Collaborative research addressed
- FDA regulated research meets FDA guidelines

Risk Assessment

- Risk = a calculation of the probability and magnitude of a harm

- Minimal risk is the 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 the performance of routine physical or psychological examinations or tests (45 CFR 46.102(h)(i)).

Benefit Assessment

- A research benefit is considered to be something of health-related, psychosocial, or other value to an individual research subject, or something that will contribute to the acquisition of generalizable knowledge.
  - Money or other compensation for participation in research is not considered to be a benefit, but rather compensation for research-related inconveniences.

Risk Category: Adults

- IRBs should assess one of the risk categories for adults ≥ 18:
  - Research not involving greater than minimal risk
  - Research involving greater than minimal risk to subjects
  - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects
  - Research involving greater than minimal risk and no prospect of direct benefit to individual subjects

Benefit Category: Adults

- IRBs should assess one of the benefit categories:
  - No prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition
  - No prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge to further society’s understanding of the disorder or condition under study
  - The research involves the prospect of direct benefit to individual subjects

Risk Analysis: Pediatrics

- 45 CFR 46.404: Research not involving greater than minimal risk to the children
- 45 CFR 46.405: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research
- 45 CFR 46.406: Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition
- 45 CFR 46.407: Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

IRB Review:
Post Initial Approval

What Needs to be Submitted?

- Amendments
- Unanticipated Problems
- Adverse Events
- Safety/Compliance Reports
- Deviations
- COIs
- Continuing Reviews
- Status changes

To whom should these reports be directed?

- IRB → OHSRP → OHRP
- FDA/Sponsor/OBA
- DSMB
- Institute CD

Amendments
SOP #10

Reasons

- Personnel
- Safety issues
- Protocol
  - Treatment schedule
  - New drug
  - Dosage
  - Follow up schedule
- Consent/Assent

How to Amend

- Prepare memo to IRB chair
- State clearly what is to change and why
- Marked*, updated protocol
- Updated* consent/assent
- Other supporting documents as required (FDA, RSC, etc)

**track changes or bold & strikeout*

Continuing Review(CR) SOP #9

- Report on how the protocol is going:
  - Any new developments in alternatives?
  - Risks and discomforts haven't changed?
  - Benefits haven't changed?
  - Any new risks identified?
  - Are the initial statistical assumptions still valid
  - Have any/all amendments been incorporated into the protocol and IC document?
- Protocols must be reviewed annually, or as appropriate to risk - decision made by the IRB
  - Suggest submission early, ~2 months to avoid a lapse in approval

CR: What is Submitted…

- Continuing review application, includes
  - Inclusion enrollment report
- Latest IRB approved protocol and consent/assent forms
- Aggregated summary report:
  - UPs
  - Deviations
  - All Unanticipated Adverse Device Effects (UADE)
  - All Adverse Events (AEs) (including expected AEs, except those specified in the protocol and approved by the IRB as not reportable)

…CR: What is Submitted

- Any information in the literature, or evolved from similar research, that might affect the IRB's analysis of risk/benefit for the protocol.
  - If such information is obtained before the time of continuing review, it should be reported to the IRB at the time that it becomes known, and summarized at the time of continuing review.
- A summary of any research-related complaints from subjects.

Expedited Review
SOP #7A

- An IRB may use the expedited review procedure to review either or both of the following:
  - Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk
  - Minor changes in previously approved research during the period (of one year or less) for which approval is authorized

Examples of Common Expedited Reviews…

- Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture
- Prospective collection of biological specimens for research purposes by noninvasive means
- Collection of data through non invasive procedures
- Research on existing data, specimens, materials collected for n*on-research* purposes
- Surveys/questionnaires
- When IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified

…Examples of Common Expedited Reviews

- Continuing Review when
  - Research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or
  - where no subjects have been enrolled and no additional risks have been identified; where the remaining research activities are limited to data analysis

IRB Record Keeping

- What needs to be maintained
  - Copies of all protocols
  - Samples of approved consent documents
  - Correspondence with investigators
  - Board procedures
  - IRB meeting minutes
- Records are subject to inspection by authorized member of the department or agency
- Records must be maintained for 3 years after protocol terminated

MORE NIH IRP SPECIFICS

NIH's FWA

- 1 FWA for 12 NIH IRBs
  - Each with different perspectives and SOPs
  - FWA#: 00005897, Expires: 2/25/2014
- Granted to:
  - Michael M Gottesman, MD

    Deputy Director for Intramural Research

NIH Intramural IRBs…

- National Cancer Institute (NCI)[1]
- National Heart Lung and Blood Institute (NHLBI)[2]
- National Institute of Allergy and Infectious Diseases (NIAID)[1]
- National Institute of Child Health and Human Development (NICHD) [2]
- National Human Genome Research Institute (NHGRI) [2]
- National Institute of Diabetes and Digestive and Kidney Diseases and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIDDK/NIAMS) [2]

[1] iRIS
[2] PTMS

…NIH Intramural IRBs…

- Combined Neuroscience (CNS) *(red, white, blue, purple panels)* [2]
  - National Institute of Neurological Disorders and Stroke (NINDS)
  - National Institute of Mental Health (NIMH)
  - National eye Institute (NEI)
  - National Institute on Deafness and other Communication Disorders (NIDCD)
  - National Institute of Dental and Craniofacial Research (NIDCR)

[2] *PTMS*

…NIH Intramural IRBs

- National Institute of Environmental Health Sciences (NIEHS) *in North Carolina*[2]
- National Institute on Aging (NIA) *Medstar IRB in Baltimore*[2]
- National Institute on Drug Abuse (NIDA) and National Institute Alcohol Abuse and Alcoholism (NIAAA) *in Baltimore*[2]

[2] *PTMS*

NIH Resources & IRB Related Committees

- OHSRP's website
  - https://federation.nih.gov/ohsr/nih/
- IRB Professional Administrators Committee (IPAC)
- Human Subjects Research Advisory Committee (HSRAC)

NIH Protocol Applications

- Protocol Resource Impact Assessment (PRIA)
- Form 1195
- Form 1195-1
- All forms found at OPS website: http://intranet.cc.nih.gov/ops/forms.html

CCR Resources

Protocol Support Office

- Provides regulatory support throughout the protocol lifecycle to CCR Investigators and their research team
- nciprotocolsupportoffice@mail.nih.gov

IRB Administrative Office

- Provides administrative support for the NCI IRB
- IRB Chair: J. Michael Hamilton, M.D.
- https://ccrod.cancer.gov/confluence/display/CCRCRO/IRB+Administrative+Office
- nciirbadmin@mail.nih.gov

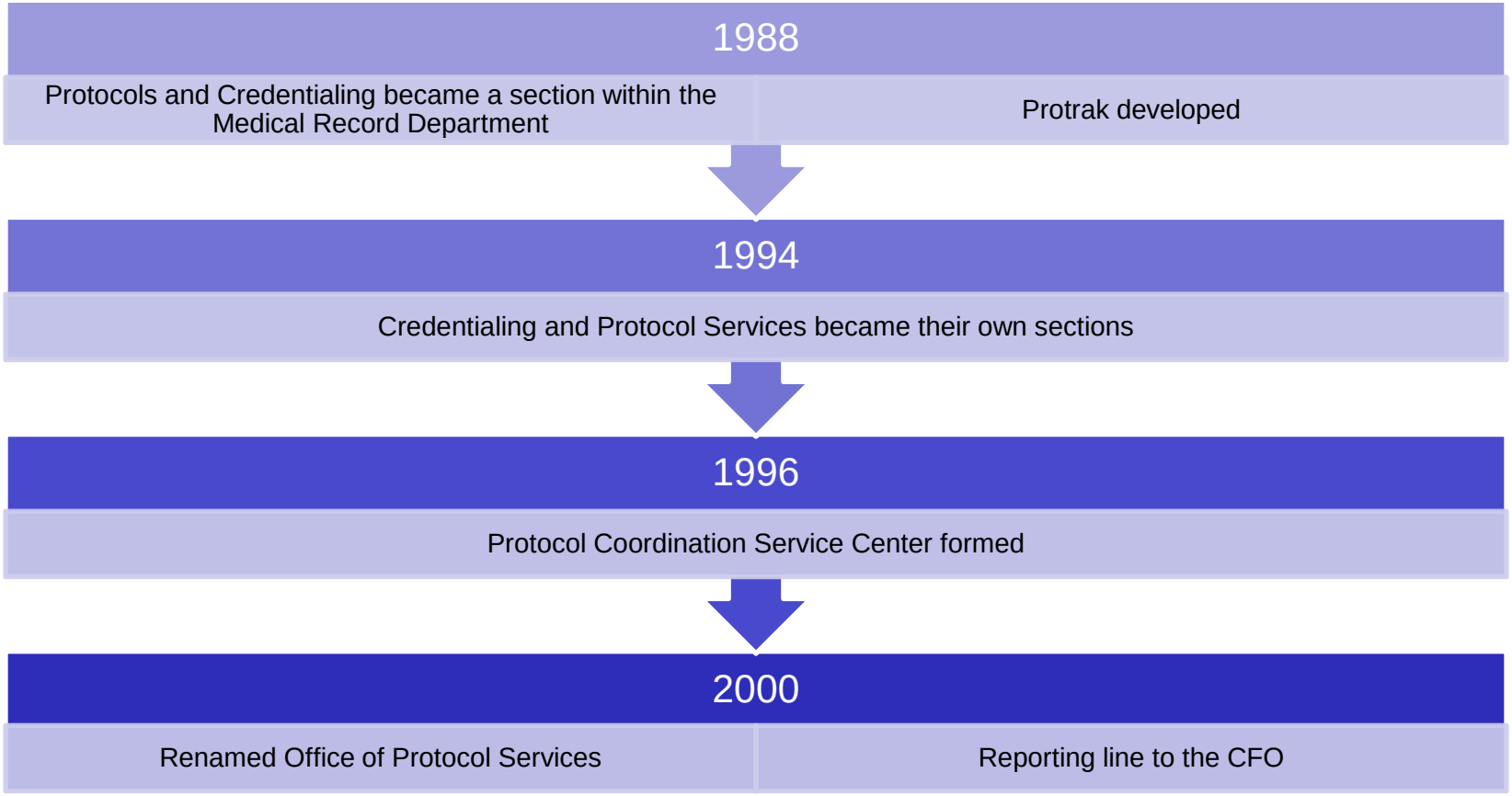
PSO Goals

- Facilitate the writing of scientifically valid, internally consistent protocols
- Decrease administrative and regulatory stipulations
- Move protocols quickly through approval process
- Manage INDs on behalf of PI Sponsors
- Allows Research Nurses more time for protocol management (i.e. research documentation and QA) and patient support

PSO Services Provided

- Regulatory coordination
- Protocol writing
- SRC/IRB submissions
- FDA submissions
- Other submissions
- Minutes for CCR meetings
- Administer Scientific Review

Office of Protocol Services (OPS): Background



Functions of OPS…

- Maintain intramural program data repository “Protrak”
  - Contains ~1900 active protocols and ~7800 inactive protocols
  - Over ~ 400 data fields
- Conduct a Quality Review of Actions/Abstract data into Protrak
  - Last step in the review process
  - Review for NIHCC/policy/NLM requirements are adhered to
  - Resolve discrepancies with Protocol/IRB Coordinators
  - Update Protrak
  - Route initial protocols to Director, CC/DDICR
  - Assign protocol number
    - Year approved by IRB
    - Institute
    - Sequential #
- Process 420 protocol actions per month

…Functions of OPS

- NIH CC Studies
  - Post consent documents to NIH Clinical Research Studies Active consent/Assent Documents website
  - ~580 consent documents sent monthly
  - Maintain Short-form Consents available in 41 different languages

Services…

- Generate Cumulative Accrual Reports
  - BTRIS provides ability to validate and generate cumulative enrollment reports
    - http://btris.nih.gov
- Generate ad-hoc reports from Protrak
- Respond to Inquiries
- Notify CC Departments monthly of new/terminated protocols

…Services…

- Update protocol websites/databases via feed to the CC Data Warehouse:
  - Clinicaltrials.gov
  - NIH CC Search the Studies
  - Protocol Query System
  - BTRIS
  - CRIS
  - ATV System
- Provide guidance and consult on issues related to the protection of human subjects research/NIH or CC policies procedures

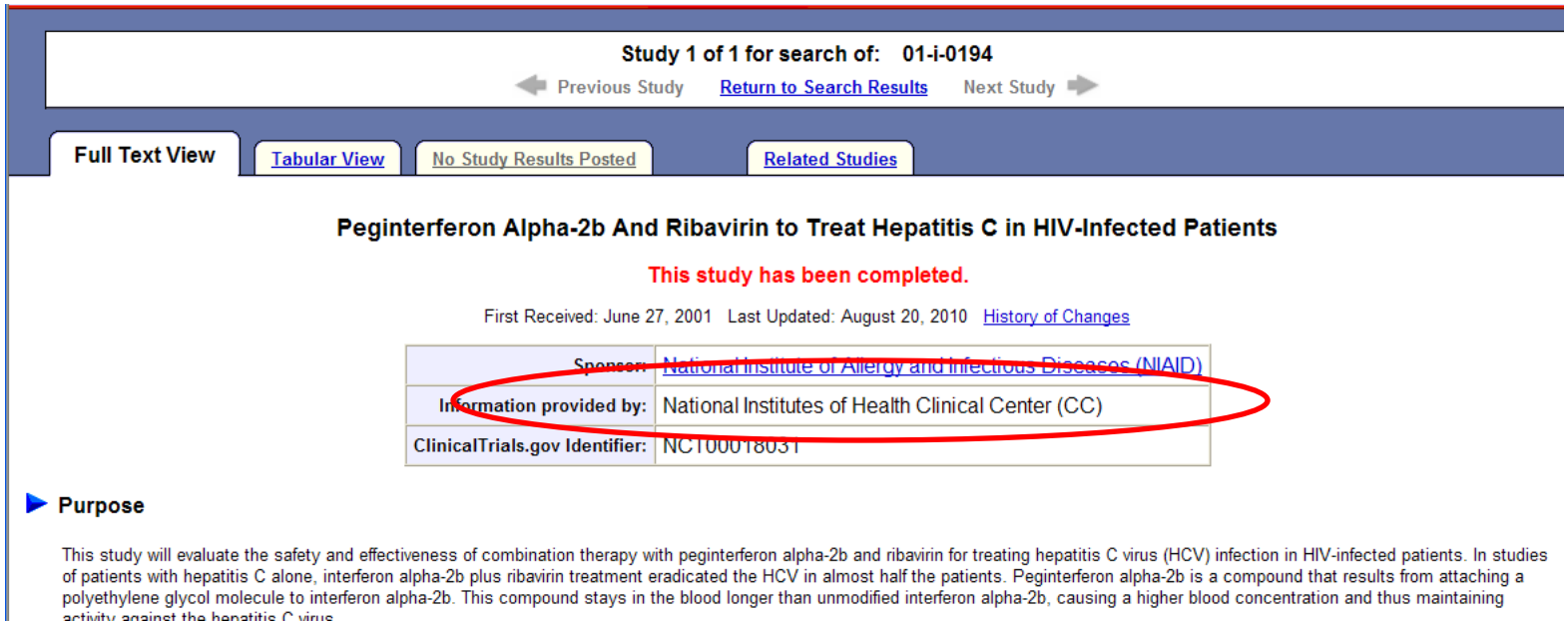
…Services

- Intramural Representative for Tracking and Inclusion Compliance
  - Serve on committees/workgroups related to tracking and inclusion
  - Analyze policy implementation
  - Generate data reflecting participant accrual by Ethnicity-Race-Gender annually for Congressional reporting

Role of OPS in Complying with FDAAA

- Serve as the Intramural Liaison for Clinicaltrials.gov
- Register Protocols
- Serve as Administrator for Protocol Registration System (PRS)
- Confirm “Responsible Party” with PI
- Monitor for Compliance

Protocols Posted by NIHCC



Study 1 of 1 for search of: 01-i-0194

Previous Study | Return to Search Results | Next Study

Full Text View | Tabular View | No Study Results Posted | Related Studies

Peginterferon Alpha-2b And Ribavirin to Treat Hepatitis C in HIV-Infected Patients

This study has been completed.

First Received: June 27, 2001 Last Updated: August 20, 2010 History of Changes

Sponsor:	National Institute of Allergy and Infectious Diseases (NIAID)
Information provided by:	National Institutes of Health Clinical Center (CC)
ClinicalTrials.gov Identifier:	NCT00018031

Purpose

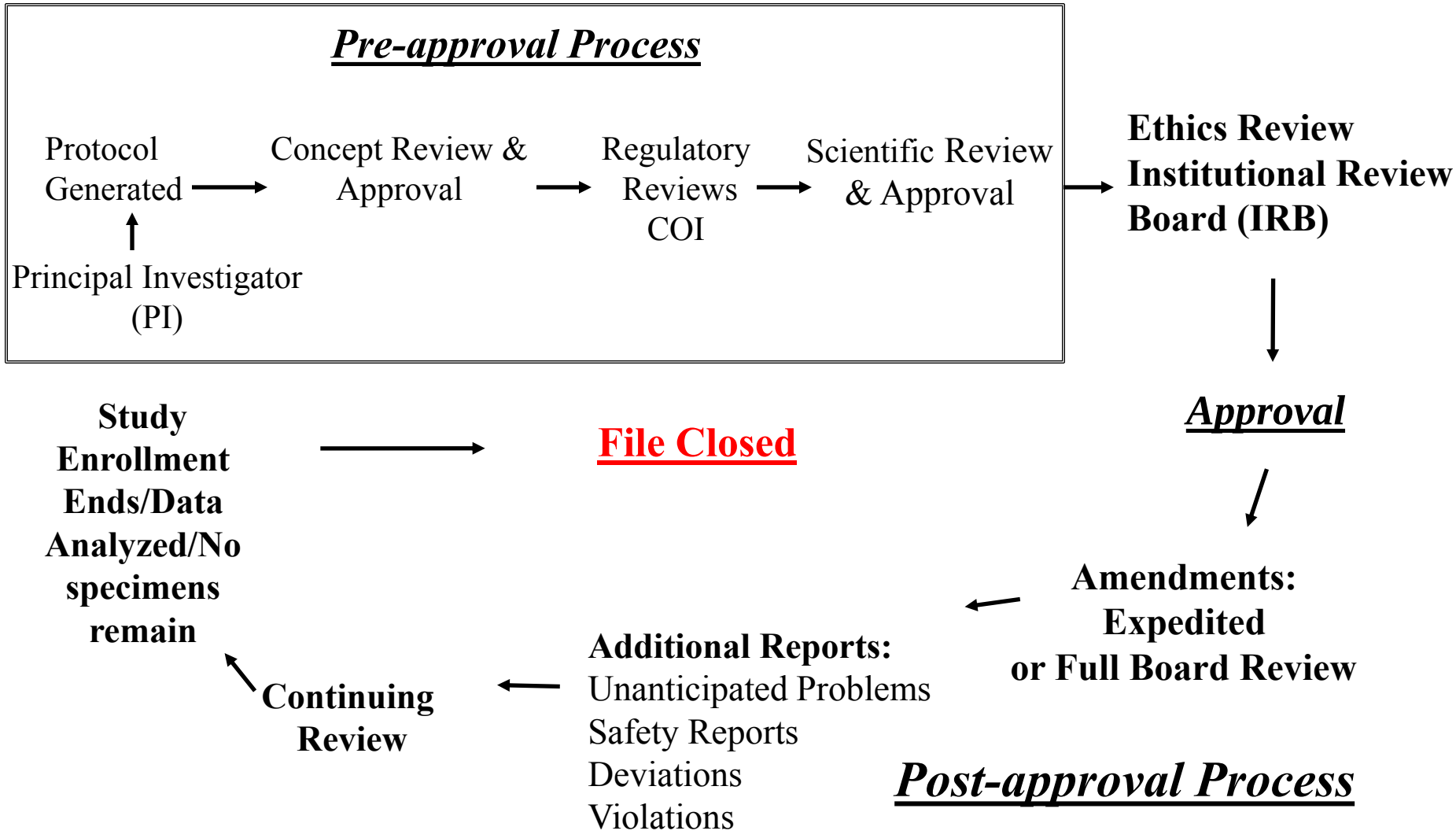
This study will evaluate the safety and effectiveness of combination therapy with peginterferon alpha-2b and ribavirin for treating hepatitis C virus (HCV) infection in HIV-infected patients. In studies of patients with hepatitis C alone, interferon alpha-2b plus ribavirin treatment eradicated the HCV in almost half the patients. Peginterferon alpha-2b is a compound that results from attaching a polyethylene glycol molecule to interferon alpha-2b. This compound stays in the blood longer than unmodified interferon alpha-2b, causing a higher blood concentration and thus maintaining activity against the hepatitis C virus

Updating Protocol Information

- Nightly feed from Protrak
  - Continuing review/Amendments
  - Request of research team
    - CC_Protocol_Services@cc.nih.gov

- If ownership of the protocol record has been transferred in the PRS, responsibility defaults to RP/designee

Protocol Life Cycle



Questions

Thank you to Kim Mitchell, Director OPS, for the use of her OPS slides.