What Investigators Need to Know About Scientific Review of New and Ongoing Protocols

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NIH Intramural Research Program
Our Research Changes Lives

one program
many people
infinite possibilities

Objectives:

- Provide an overview of the Intramural Research Program scientific review process and purpose
- Briefly describe the Chief Scientific Officer role related to IC protocol reviews
- Describe the scientific review policy for initial new and ongoing research protocols
- Understanding the policy process basics for protocol submission types: Initial new, waiver, annual merit review, quadrennial merit review and modifications

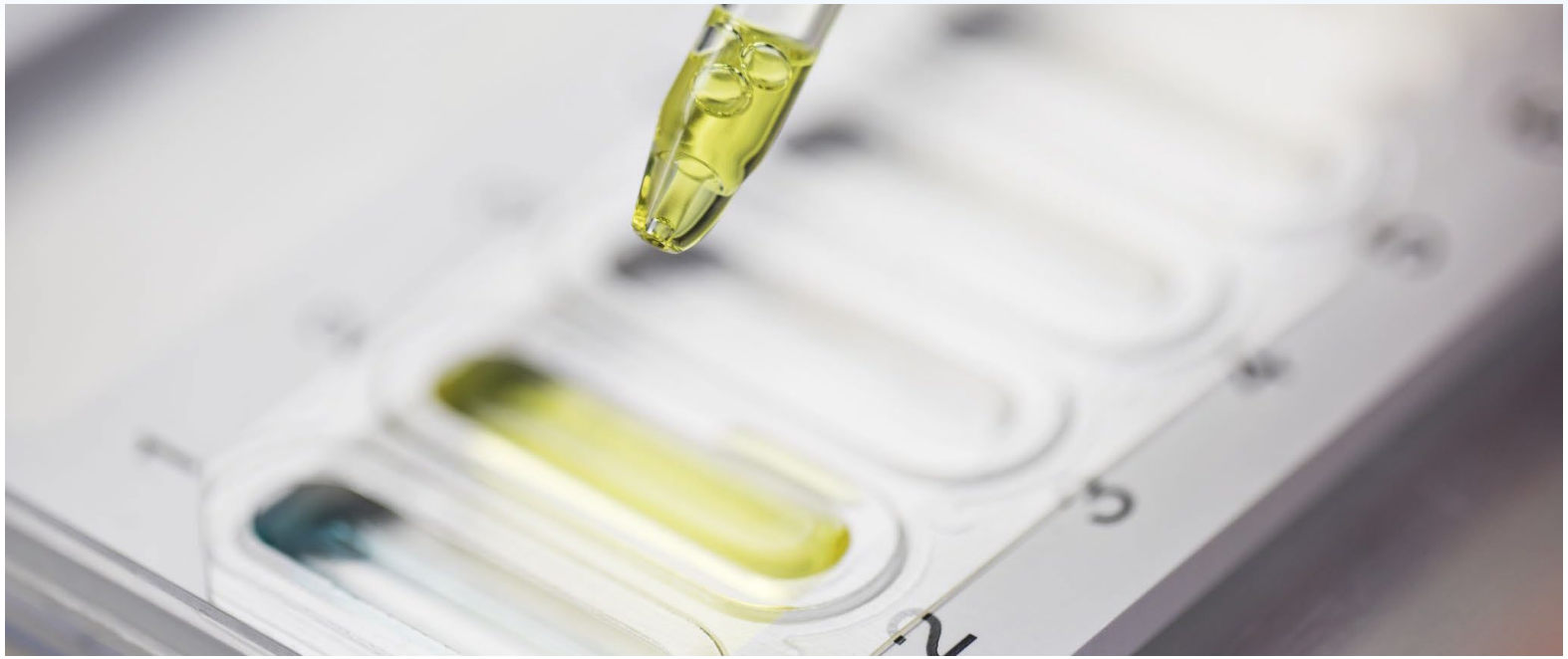
Chief Scientific Officer

Role with Scientific Review

Chief Scientific Officer/Scientific Director CC

- Provides scientific and administrative leadership for ongoing research at the Clinical Center
- Manages scientific review process for clinical protocols conducted in the NIH Intramural Program.
  - 18 institutes and centers use the hospital services.
- Coordinates scientific activities and evaluates the progress
  - Use of CC resources is also assessed by CC CD (Colleen Hadigan, MD) through the PRIA process.
- Reviews new and ongoing scientific research.
- Reviews and revise policies and procedures for the scientific review of all intramural clinical protocols research funding opportunities and the Clinical Center Board of Scientific Counselors.
- Ensures compliance with clinical trial registration and results Information Policy (3007 - Clinical Trial Registration and Results Information Reporting (nih.gov))

Overview IRP Scientific Review (SR) Process



Research Definition

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. (45CFR46.102(l))
(Education and Training (nih.gov))

A **Scientific Review** involving human subjects is an independent and thorough assessment of the quality, importance, and feasibility of the project. Ensures that specific items are covered: DMS, Patient engagement. https://www.ncbi.nlm.nih.gov/books/NBK43564/)

Internal Review Board (IRB) were created to ensure human subjects protection, informed consent for participants, ensure protocols are beneficial and had low risk.

Ethics Review- Document real potential COI.

Research History

Declaration of Helsinki (1964) adopted by the World Medical Assoc. (WMA) related to research ethics.

Nuremberg Code (1947) initial statement relates to human experimentation of the ethical principles.

- Respect of individuals
- Right to make informed decisions
- Recognition of vulnerable populations

Tuskegee Syphilis Study US PHS research started in 1932 to 1972. No informed consent, black men with low incomes tested.

- Violation of ethical standards in biomedical research study in the US.

Belmont Report: (response to the Tuskegee syphilis study).1979 *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*

- Protection from harm
- Any research protocol weighs the risk to human subjects
- Goal – benefit participant

Regulations

45 CFR 46: HHS regulations as a result of Belmont Report. Requirements in place for HHS supported and conducted research. IRB compliance and regulations and informed consent to protect human subjects with additional protection consideration.

- Subpart B – research with pregnant women and fetuses
- Subpart C – Research with prisoners
- Subpart D – Research with Children

Common Rule Subpart A revision a few years ago related to informed consent, exemptions, biospecimens/data, the “reasonable person” standard informed consent form (ICF), Posting ICFs, Broad consent (not implemented at NIH) requirements.

Scientific Review Purpose

- Scientific review varies by IC. Usually begins with the initial concept and full protocol review

- Assessment
  - Are you asking an important question?
  - Is your approach appropriate?
  - Is the project feasible?
  - Do you have the training/resources needed?
  - Do you have a Data Management Plan?
  - Do you have a patient engagement plan?

- Study types that require review: Clinical trials; non-interventional (natural history); screening; repository, quad reviews and major amendments

- The SR process also reviews the Clinical Center usage and scarce resources to ensure best science.

SR Process for Intramural Research at Clinical Center

- Policy provides a minimal requirement for SRs
- NIH intramural ICs have further guidance and expectation for their SR process
- A scientific review is separate from the IRB (outcome letters are uploaded in PROTECT) when submitting IRB review.
- As a PI, ensure you are following the SR policy and emphasize the science with each element.

NIH Scientific Review Policy and SOP
https://clinicalcenter.nih.gov/chief_scientific_officer/scientific_review_process.html

Overall Protocol Assessment Rating

ICs committee review provides scoring

- A numerical score is also given: 0 = Poor to 10 = outstanding.

  Policy states:

  Overall Protocol Assessment Rating: In each committee, members should rank the overall scientific merit of the protocol on a scale of 1-10, 10 being the highest score. This should be obtained by anonymous/secret ballot and tallied with an average overall score by the SR coordinator. This numerical score should be entered into PROTECT in the "submit committee review" activity.

- A rating score is not required for quadrennial reviews.

Reviewer Committee Selection

- ICs have Scientific Review Committees with further IC specific guidance

- Experts in research are selected for committees, such as Scientist, Statistician, Bioethics, etc.

- May consider extramural or non-NIH reviewers
  - Conflict of Interest form completion required, Microsoft Word - BSC Reviews Conflict of Interest.docx (nih.gov)

Scientific Review Policy for initial new and ongoing research protocols

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Scientific Review (SR) Policy Reviews

Concept Review at department/lab/branch level – provides background, objectives, design, eligibility, statistical section and references

- Review feasibility
- Meet the mission of the lab/branch

Initial New Protocol Scientific Review

- ✓ Protocol is review prior to IRB submission
- ✓ ICs create guidance for their committee
- ✓ Experts of research subject matter

SR Policy Reviews (cont'd)

Modification (Amendment) Reviews

Review for changes that affect a scientific question(s) or scientific approach.

Waivers from Scientific Reviews

Some research projects that are secondary research (retrospective analysis, sample study)

Expedited Reviews

Phase II/III; multi-center already reviewed had a SR

Tip: Have a copy of the PROTECT SR specific questions to help guide your SR submission.

Protocol Types

Intramural Research Protocol Reviews can be:

- ✓ Initial Reviews
- ✓ Expedited Scientific Reviews
- ✓ Waivers from Scientific Reviews
- ✓ Modification Reviews (significant changes)
- ✓ Annual Merit Reviews
- ✓ Quadrennial Reviews

Chief Scientific Officer website SR policy: Office of the Chief Scientific Officer | Clinical Center Home Page (nih.gov)

Clinical Trial

Non-interventional observational studies (natural history)

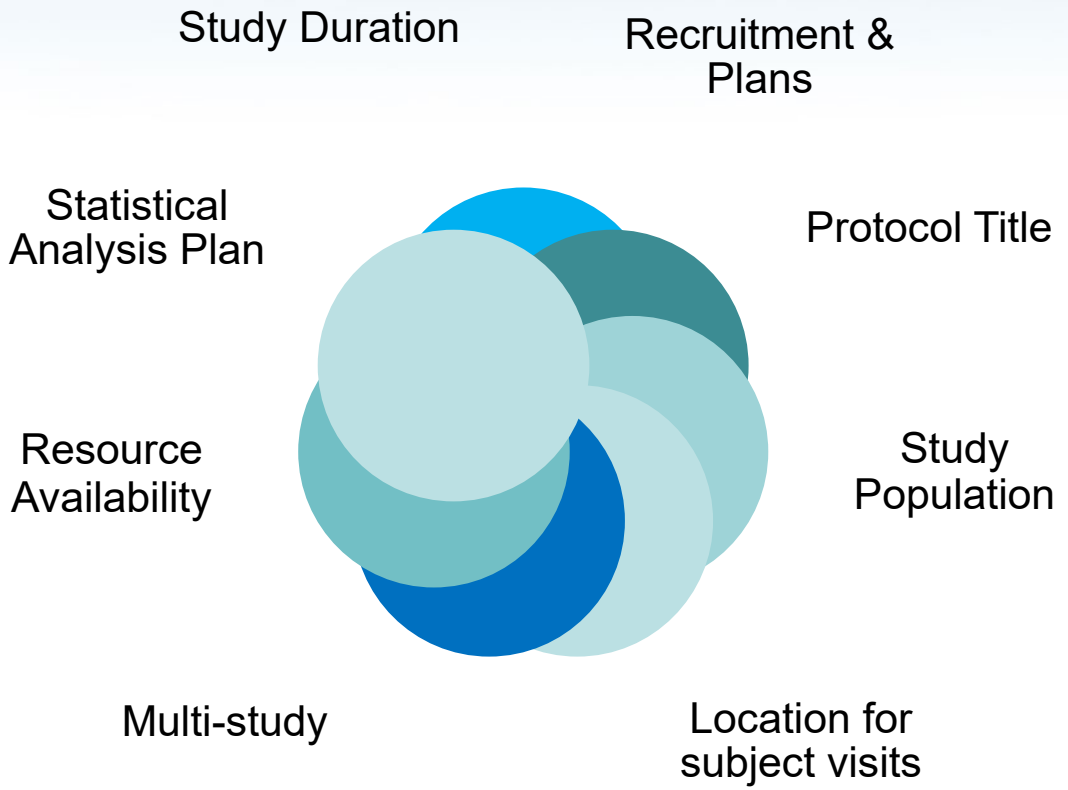
Screen protocols

Repository protocol

Scientific Review Protocol General Elements

The General Elements:

- 45 CFR 46: HHS regulations protect human subjects
- HRPP Policy 400 – Protections for Vulnerable Population.
- Consider objectives/endpoint to ensure question is answered and human safety is preserved.
- Valuable to have statistician review protocol plan.
- SR preparation consider the “science and impact with the protocol”.



Initial SR of Studies

Clinical Trial, Interventional Studies

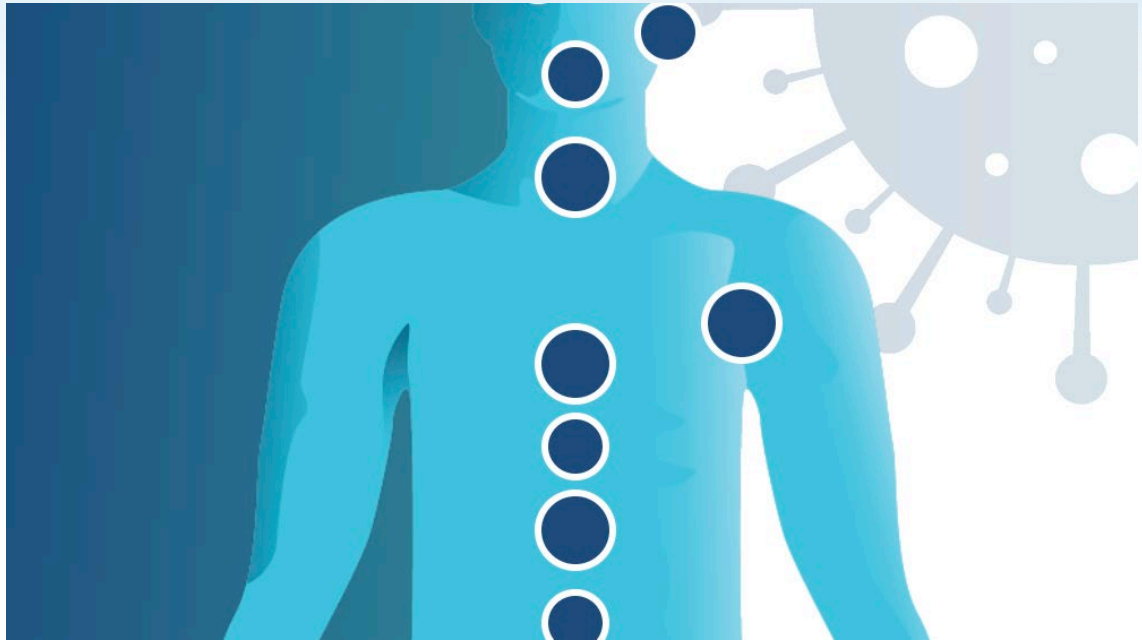
- Describe phase, drug description, delivery methods, etc.
  - Methods of study – i.e. randomized, cohorts, etc.
- HRPP 400 -Compliance with Inclusion of Women and Minorities policy guidelines
- Provide additional information such as Investigational product, IND/IDE and/or FDA study.
  - *Policy 500 Series – FDA Requirements for Human Subjects Research and Data and Safety Monitoring.*
  - Whether require IND/IDE (ORSC Regulatory Support Section)
- Discuss Endpoints
- Pre-clinical data

(cont'd)

Observational Studies

- Define objective of the study.
- Level of care provided to subjects.
  - Examples - Sample studies, observational studies

Long-term COVID studies



https://covid19.nih.gov/covid-19-topics/long-covid

Protocol Elements (cont'd)

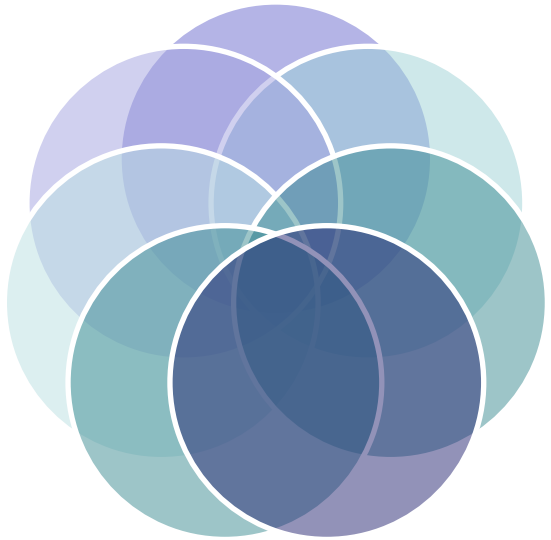
Clinical Monitoring Plan

Verifies conduct of study, documentation are followed with intramural SOPs, GCP, HSRP requirements

Person/entity responsible for monitoring

Data & Safety Monitoring

Type/frequency of planned visits



Plan for deficiencies if cases arise

Overall description of consent and documentation

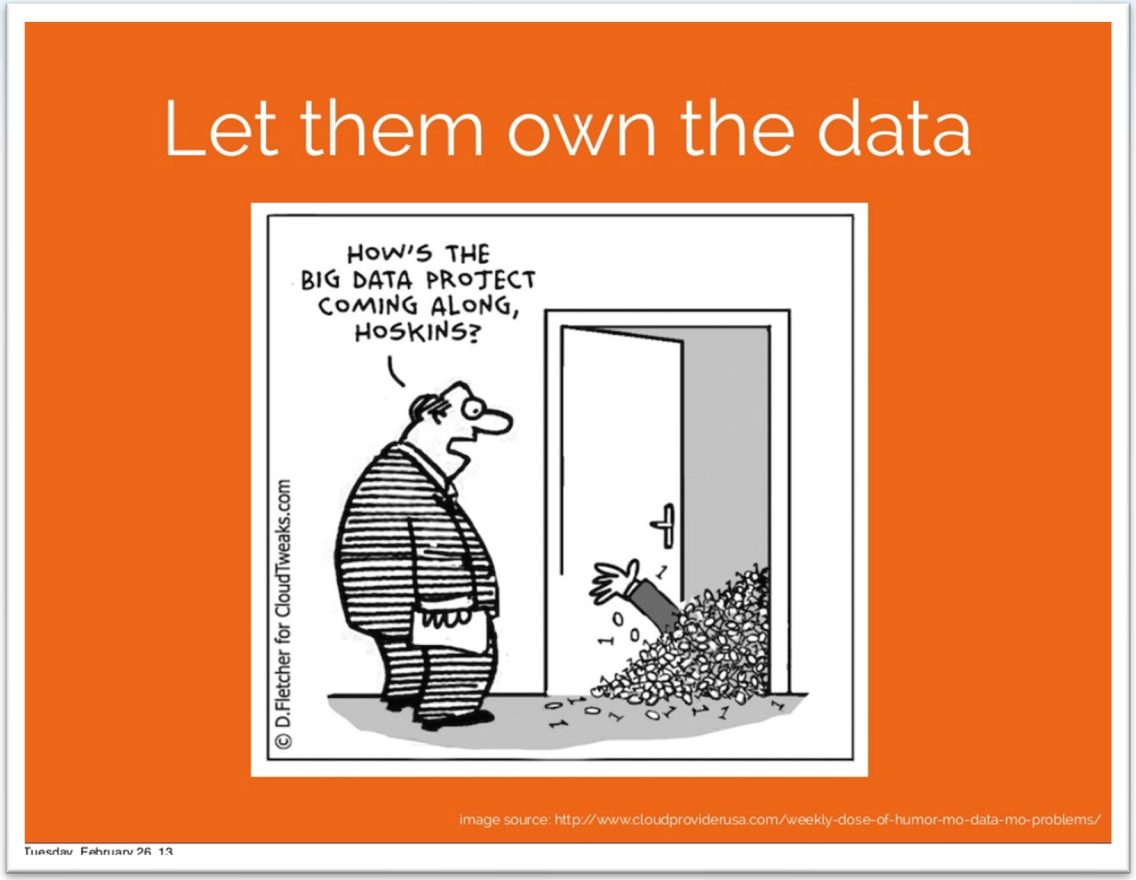
Describe monitoring of labs, pharmacies, etc.*

Record and management of reportable events

Monitoring Plan (cont'd)

- **Data Access and Sharing & Common Data Elements** –ensure human data sharing polices are in place and Genomic Data Sharing policy.

- Methods described for data collection database. FDA, 21CFR Part11 compliant, case report forms, data validation.



Data Access and Sharing Plan & Common Data Elements Applicability

Describe data sharing policy and ensure following new policy guidelines,(1/25/2023)
https://oir.nih.gov/sourcebook/intramural-program-oversight/intramural-data-sharing/2023-nih-data-management-sharing-policy,

ClinicalTrials.gov results reporting requirements (42CFR11) and NIH Policy for NIH Funded Clinical Trial Information,
https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-149.html

NIH Genomic Data Sharing Policy,
https://osp.od.nih.gov/scientific-sharing/policies/

Use of CDEs support NIH Data Management, http://cde.nih.gov/

Protocol Elements (cont'd)

Milestone Plan

- Address the timeline and proposal for the protocol.
- The focus depends on trial type (details of enrollment, randomization, plan for accrual, and completion of endpoints, etc.)
- Objectives with milestones are concise - lifecycle of the study.
- Clinicaltrial.gov final reporting.
- Annual and quadrennial reviews address plan.

Protocol Elements (cont'd)

Clinical Protocol Schedule of Events (i.e. Week 2, 4, 6 and 8 visits – clinic, lab, scans, etc.)

- Review will assess if can be accomplished in a timely manner
- Any issues with completion
- Refer to IRB templates.

▷ Statistical Analysis Plan

- Refer to IRB templates.
- Focus on enrolled accrual and methods plan to use for expected size
- The plan is more detailed for Phase III clinical trials.

Protocol Elements (cont'd)

Disease Community Engagement and Study Design

- Address disease community engagement of research participants in the study design.
- Did you include the research population perspectives for the outcome determination?
- If you are considering a protocol with rare disease, may want to explore support organizations related to disease or diagnosis.
- If using disease community engagement, define the NIH process for engagement (conflict of interest certification form)

Protocol Elements (cont'd)

Investigator Qualifications

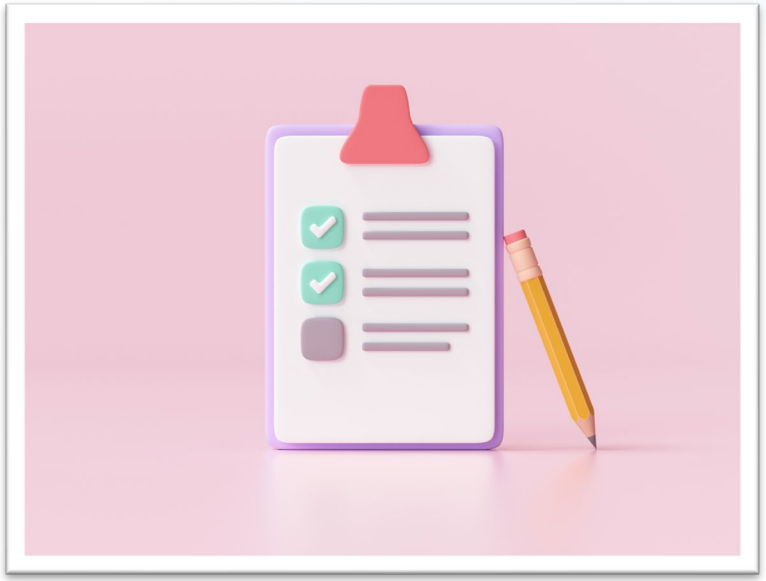
ENSURE INVESTIGATOR IS QUALIFIED AND TRAINED

CURRICULUM VITAE

HRPP Policy 3014-300 Investigator responsibilities [3014-300 - Investigator Responsibilities (nih.gov)]

Understanding the policy process basics for protocol submission types: waiver, annual merit review, quadrennial merit review and modifications

Expedited Reviews



- Expedited reviews will be done if IC committee or Chair deems appropriate.
- Phase II/III multicenter
- Chair or SR committee review and approve in PROTECT.
- Justification for expedited review with outcome letter.
- Scientific Director or Clinical Director approve in PROTECT as ancillary review after Chair approves.
- CSO reviews after sign-offs complete.
- Final letter sent to team once CSO approves.

SR Waiver Request

- Retrospective analysis, data analysis/repository (collecting samples); Tissue collection.
- The PI provides a rationale for waiving a scientific review.
- Committee Chair reviews along with approval of Clinical Director, Scientific Director of the IC.
- Once approved by Chair, forwarded to CSO for approval.
- Final approval letter sent to team after CSO signs off in PROTECT.

Modification (Amendment) Substantive Changes SR

Review required when a change affects a scientific question(s) or change in the scientific approach, trial design or analysis.

Important to show what learned to date with objectives and data

Change in risk level to protocol.

Scientific Reviews – Annual and Quadrennial Merit

IC developed a guidance plan for Merit review process.

- Annual Scientific **Review** (open/accruing subjects).
- A **Quadrennial review** (open/accruing subjects).
- Not necessary for closed to accrual but open for analysis

Quadrennial review requires DMS plan addressed for secondary research protocols.

Annual Scientific Merit Review

- ✓ Is the science relevant and accruing appropriately?
- ✓ What does the enrollment look like to date (consider age is after 1/25/19 to coincide with NIH Inclusion Across the Lifespan Policy)?
  - Cumulative Inclusion Enrollment Report (CIER) included in PROTECT.
- ✓ Review the benefit of the research.
- ✓ Summary of adverse events to review.
- ✓ Discoveries in the field that may have altered the protocol direction.

Quadrennial Review

- What has the study done in the past 4 years
- Elaborate on the plan for the next 4 years or considerations
- Review resources and staff usage (research team, data managers, outside vendors)
- Committee meeting to include PI presenting study progress.
- PI provides written report

***ICs have further specific guidance on quadrennial reviews.**

Committee Members

- Chair, Executive Secretary/Coordinator and Committee Members
- Two reviewers from IRP outside the lab/branch or IC department
- A statistician member
- Ethics member
- Invite Experts if rare disease/specialized specific disease (non-voting)

IC SR Committee Outcomes

- Protocol Approved
- Approved with recommendations.
- Protocol conditional approved with Stipulations
  - ✓ Respond to stipulations and recommendations.
  - ✓ CSO reviews protocol submissions to ensure stipulations and recommendations are addressed adequately.
- Protocol disapproved with Stipulations
- Disapproved
- Outcome letters reflect meeting minutes & outcome.

IRB PROTECT Specific Questions

Enter a ticket in JIRA

Enter a ticket in JIRA and a member of our PROTECT Core Team will reach back out to you as soon as possible to assist.

Visit our virtual “Help Desk”

Members of our PROTECT Core team will be available via Zoom for help.
Join the Zoom meeting to have your questions answered.
Monday, & Wednesday from 10:00 – 12:00
Tuesday & Thursday from 1:00 – 3:00
Link to Zoom Meeting: Click here to join the meeting
Outside of these hours, submit a Jira ticket for one on one assistance.

PROTECT Help center Link at
https://irbo.nih.gov/confluence/display/ohsrp/OHSRP+PROTECT+Help+Center

Office of Research Support and Compliance (ORSC)

Protocol Navigation Section
Eugene Bond, CCRP
Sara Sadeghi, CPC
Email ORSCProtocolSupport@cc.nih.gov

IND/IDE Support Section
Lisa C. Goldfeder, RAC, CCRP
Email REGSupportORSC@cc.nih.gov

Office of Protocol Support
(Questions related to SR & CSO review process)
Kim Mitchell
Email CCScientificReview@cc.nih.gov

Clinical Research Quality Management
Alissa Mun, MS, ACRP-CP®
Email: alissa.mun@nih.gov

Protocol Coordinator Section
Stephanie Burrison, MSN-RN, ACRP-CP®
Email: stephanie.burrison@nih.gov

Thank you!

References

Goodyear, M. D., Krleza-Jeric, K., & Lemmens, T. (2007). The Declaration of Helsinki. *BMJ (Clinical research ed.)*, *335*(7621), 624–625. https://doi.org/10.1136/bmj.39339.610000.BE

Institute of Medicine (US) Committee on Assessing the System for Protecting Human Research Participants; Federman DD, Hanna KE, Rodriguez LL, editors. Responsible Research: A Systems Approach to Protecting Research Participants. Washington (DC): National Academies Press (US); 2002. 3, Back to Basics: Scientific, Conflict of Interest, and Ethical Review of Research Protocols. Available from: https://www.ncbi.nlm.nih.gov/books/NBK43564/ HHS Vulnerability Disclosure

Scientific Review Standard Operating Procedures (2020); https://ocr.od.nih.gov/pdfs/SOPs_Rev_04-06-20_Final.pdf

Office of Intramural Research, HRPP Policies and Guidelines; IRBO https://irbo.nih.gov/confluence/display/ohsrp/IRBO-i

US Department of Health and Human Services, Subpart D — Additional Protections for Children Involved | HHS.gov

Office of Chief Scientific Officer, https://clinicalcenter.nih.gov/chief_scientific_officer/scientific_review_process.html

Office of Intramural Research (IRBO) Protect Help Center, OHSRP PROTECT Help Center (nih.gov)