National Institute of Diabetes and Digestive and Kidney Diseases

Initiation, Regulatory Requirements, and Statistical Design for Research Studies Conducted at NIH

Learning Objectives

1. The learner should know the difference between observational studies, clinical trials (drug and non-drug studies), and secondary data (new data from stored samples, existing data) as defined for the NIH Clinical Center and how study development differs for each.

2. The learner should understand the development process, know the timeline, and know the resources available for successful protocol development.

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Is my new study a clinical trial?

1. Does the study involve human participants?
2. Are participants prospectively assigned to an intervention?
3. Is the study designed to evaluate the effect of the intervention on participants?
4. Is the effect being evaluated a health-related biomedical or behavioral outcome?

If **YES** to all, then it is a clinical trial.

https://grants.nih.gov/policy/clinical-trials/definition.htm

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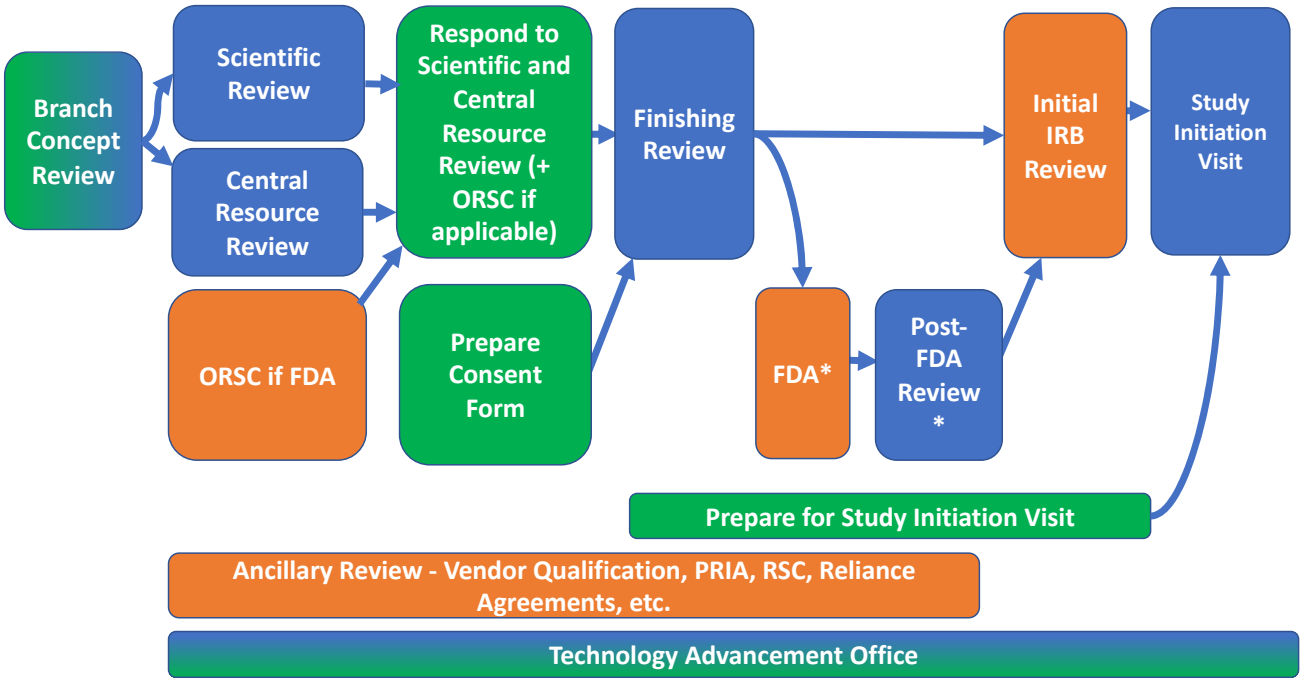
Studies at NIH CC have some unique considerations

"Patients must be assigned to an active, approved protocol in order to participate in a research study at the NIH Clinical Center **and/or receive medical care**."

(NIH CC M12-1)

NIDDK Protocol Development Process



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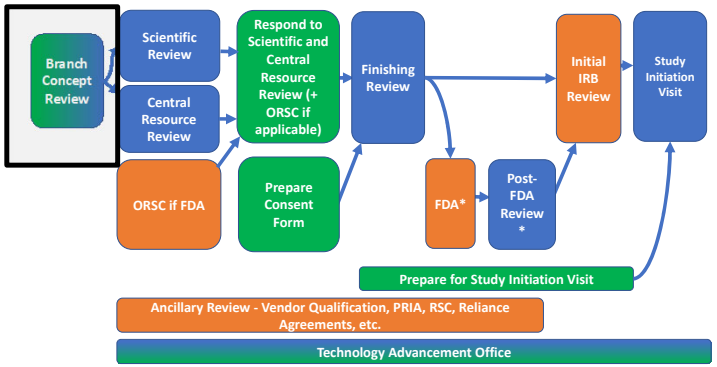
Branch Concept Review



- To your branch chief, the clinical director, and any other attendees your branch requires, present your idea for a new study:
  - Scientific background
  - Preliminary data
  - Hypothesis
  - Plan for implementation & statistical design
- Do not draft the protocol yet – get branch approval first!
- Ask branch chief to sign Attestation of Concept Review

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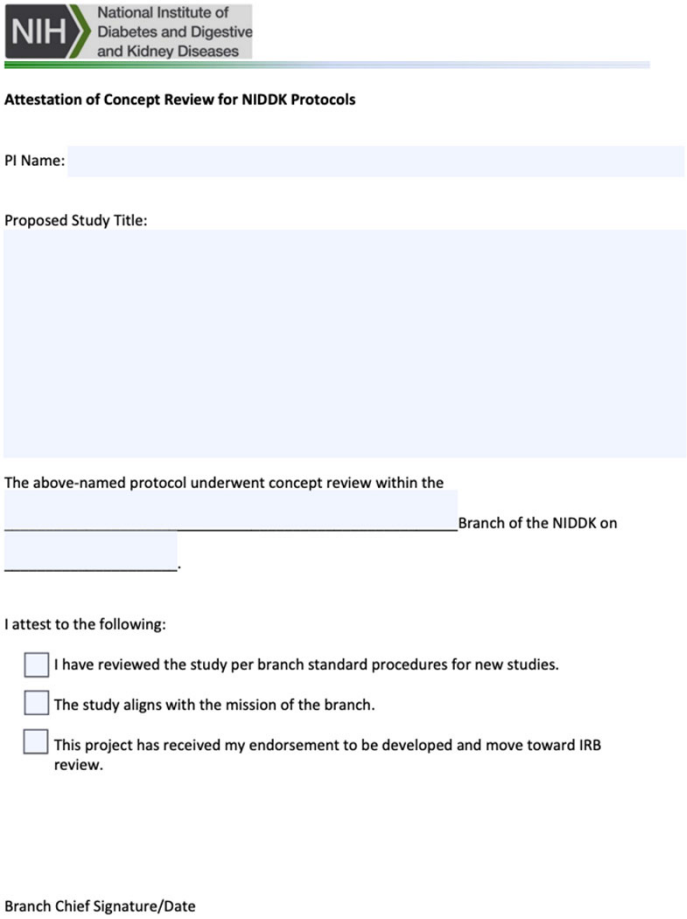
Attestation of Concept Review



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Attestation of Concept Review for NIDDK Protocols

PI Name:

Proposed Study Title:

The above-named protocol underwent concept review within the _____ Branch of the NIDDK on _____.

I attest to the following:

- ☐ I have reviewed the study per branch standard procedures for new studies.
- ☐ The study aligns with the mission of the branch.
- ☐ This project has received my endorsement to be developed and move toward IRB review.

Branch Chief Signature/Date

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Choosing an appropriate NIH protocol template

What kind of study are you planning?

Where are the templates?

Who can answer your questions?

Prospective or Retrospective?

- Will you see participants and collect new data?
  - Prospective...

- Or analyze pre-existing data and specimens?
  - Retrospective **Secondary protocol** based on other protocol(s) and consent forms

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Another possibility: Not Human Subjects Research

- When do I use this?
  - Data and samples are deidentified and I don't have access to the code key
  - I want to do a retrospective chart review in CRIS/BTRIS and HIMD has deidentified the data for me
  - I'll be collecting prospective data, and the type of research falls under the Exemptions in the revised Common Rule (and does not involve children or prisoners) [not common for NIDDK IRP]

- No IRB review required, but recommend you submit the NHSR application to IRB
  - Can be important to document IRB decision for publishing results in journals

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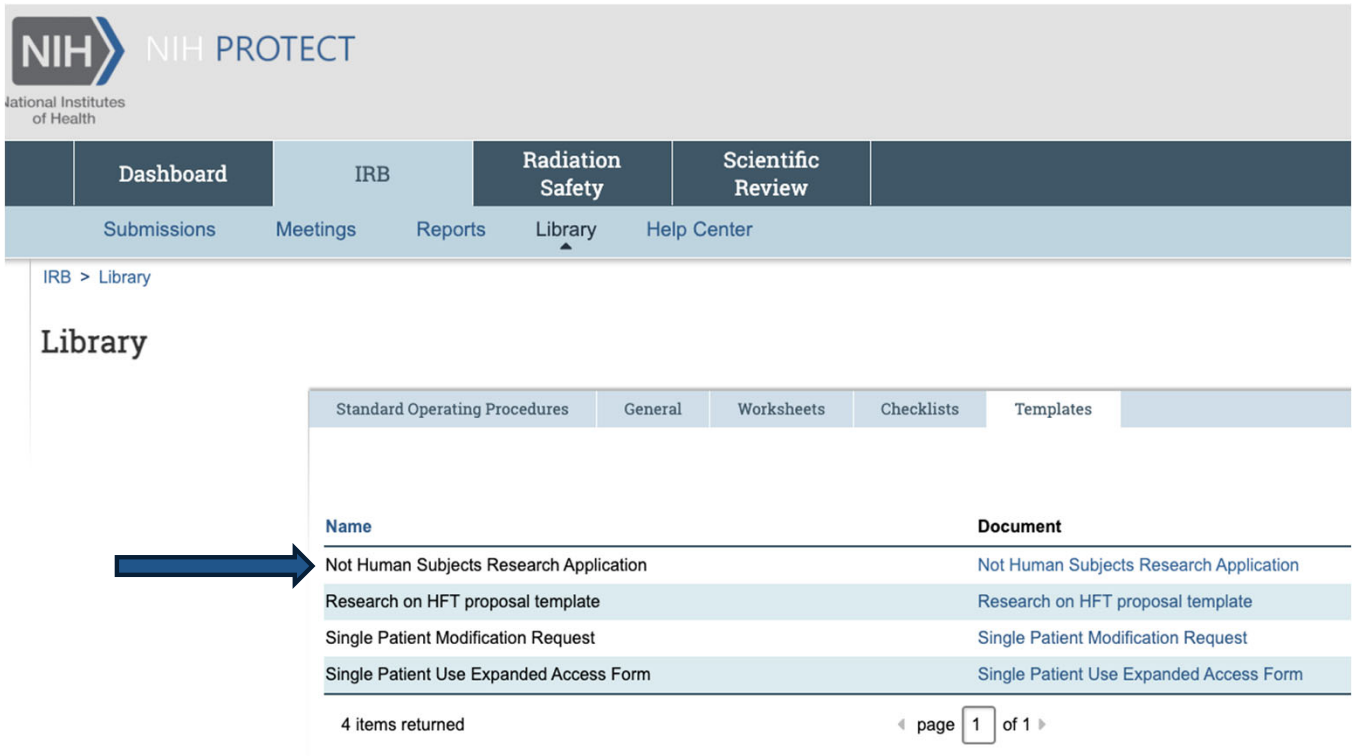
NHSR Application in PROTECT



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Next for prospective studies

- Is it a new study?

- Or is it building on to an existing study (i.e. analyzing data and samples prospectively collected for purposes unrelated to the existing study's aims)?
  - Prospective **secondary protocol**

Considerations for Secondary Protocols

- Need copies of all versions of the consent forms from the pre-existing source protocols
  - Make a table by version date and future use language (even if they were silent)

- Cannot use data or samples if the original consent stated that they'd be destroyed or barred from future use

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Next for new studies

- Will you intervene or experimentally manipulate the course of the study?
  - Interventional studies

- Or are you following the natural course of a disease and offering standard of care?
  - **Natural History/Observational protocol**
  - **Repository protocol**

Natural History or Observational protocols

- “Pre-planned observational study intended to track the course of a disease”
- Exploratory & Hypothesis-generating
- Only include research in protocol:
  - Systematic research interventions
  - Data collected during clinical care
  - Mixed clinical/research interventions

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Other considerations: observational studies with FDA oversight

- Examples: PET agents and MRI sequences can have IND/IDE designations with FDA oversight

- Use the Interventional Clinical Trial protocol template
  - Some sections may not be applicable
  - Ask navigator or protocol writer about what is required
  - Will need sponsor reporting language from NIH ORSC Regulatory Support

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Studies that Save Samples in Repositories

- Patients seen for clinical care, and research team collects extra or leftover samples and data

- Only research activities are described in the protocol!

Next for interventional studies

- Is the intervention an investigational drug or device?
  - **Interventional clinical trial template**

- Is the experimental manipulation something else – a diet, a course of counseling, etc.?
  - **Behavioral and social sciences template**

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Other considerations: Multisite studies

- Which IRB -- NIH or external?
- May need appendices for NIH-specific requirements to a sponsor-provided protocol
- Contact your protocol navigator and Shirley Rojas & Jeffrey Rollins in IRBO

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NIH Protocol Templates

https://irbo.nih.gov/nih-irb-templates/protocol-templates/

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Questions when choosing template?

- Contact your (or your PI's) protocol navigator
  - No protocol navigator?
    - Contact Joyce Linderman, Protocol Navigation Lead (lindermanj@niddk.nih.gov)

- Want more assistance with protocol development, including choosing the best template?
  - Contact Paige Studlack for the Protocol Writing Program (paige.studlack@nih.gov)

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Drafting your protocol

Work with your navigator or the protocol writing program

- Consult with NIDDK Biostats for:
  - Phrasing the Objectives & Endpoints
  - Power and sample size calculations
  - Statistical Analysis Plans

https://nih.sharepoint.com/sites/NIDDK-OfficeoftheClinicalDirector/SitePages/Biostatistics%20Program.aspx

- If FDA oversight, contact NIH ORSC Regulatory Support for:
  - Risk determinations for devices
  - Sponsor-required language

Email: REGSupportORSC@cc.nih.gov

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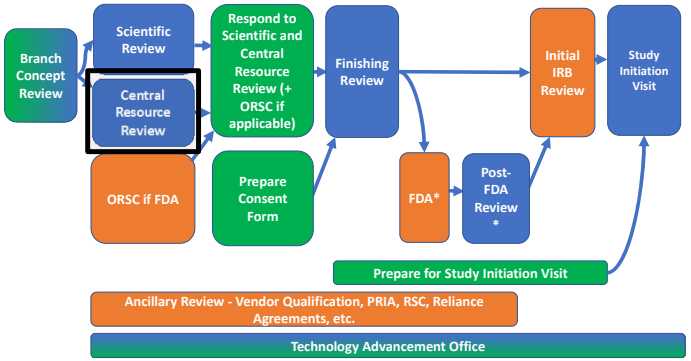
NIDDK Resource Review



- An informal meeting to discuss the protocol with the Office of the Clinical Director members (and sponsor representatives in ORSC, when there is FDA oversight).
- Focus is on centralized support for clinical research studies

not conducted for secondary studies

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Preparing for Resource Review

- Send protocol draft & Attestation of Concept Review to navigator
- Prepare a brief presentation addressing topics in Resource Review information document
- Write a standalone assessment of study risk and anticipated safety monitoring needs

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After Resource Review Meeting

- Resource Review coordinator will send a memo with action items to address from the meeting
  - Return memo with responses within 30 days or prior to NIDDK Finishing Review

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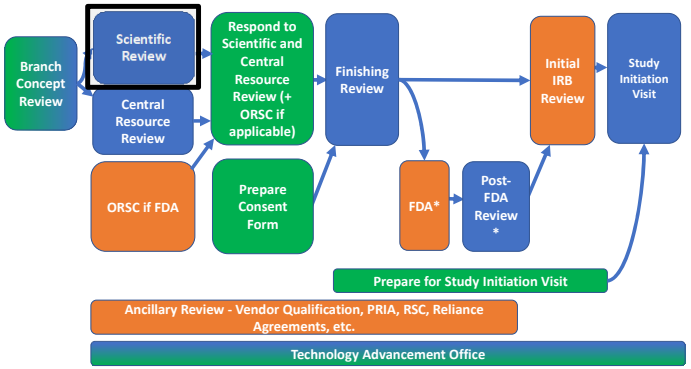
Scientific Review: Prospective Study



- Goal: obtain input from other subject matter experts (within and outside NIH) to improve study quality and rigor.
- Navigator will work with you to submit scientific review in PROTECT
- Reviewers request responses and changes to protocol

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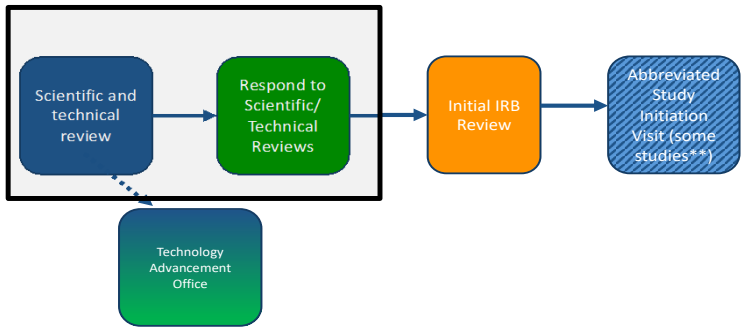
Scientific Review: Secondary Study



- Combines the resource, scientific, and finishing review into a single review process.
- Conducted internally to inform appropriate Office of the Clinical Director personnel about the study and provide finishing review comments.

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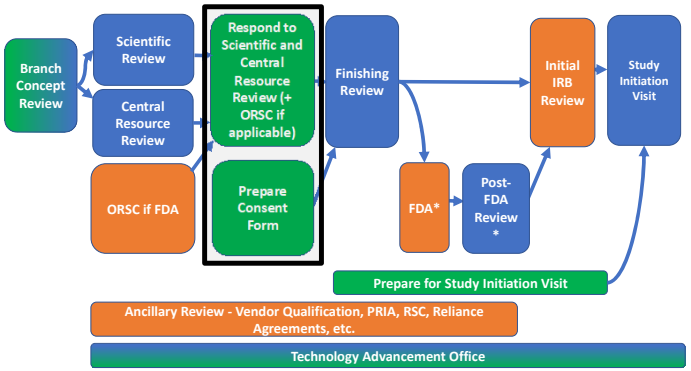
Preparing for Finishing Review



1. After you have completed the SRC process, work with your protocol navigator or writer to review the protocol for consistency and clarity.

2. Develop your consent forms.

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Finishing Review

- Aims to ensure protocol:
  - describes your research intentions & research best practices
  - aligns procedures and study objectives
  - is consistent throughout and with consent forms
  - complies with regulations & includes IRB-required elements
  - has consents written at 6-8th grade level & assents appropriate for intended ages

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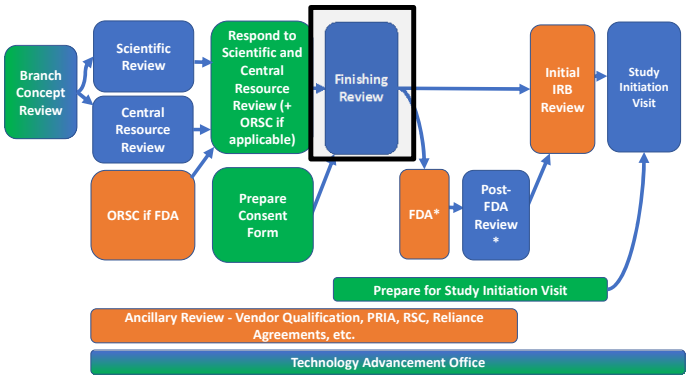
Finishing Review Process



1. Send your finalized protocol, consents/assents, and NIH appendices (if applicable) to Joyce Linderman & Paige Studlack

2. Reviewers in NIDDK OCD will return tracked changes versions of these documents & may request meetings to discuss

3. Incorporate changes or discuss rationale for not making changes with finishing reviewers → send back

4. Finishing reviewers will notify when review is complete, so you and your navigator can proceed to IRB or FDA review

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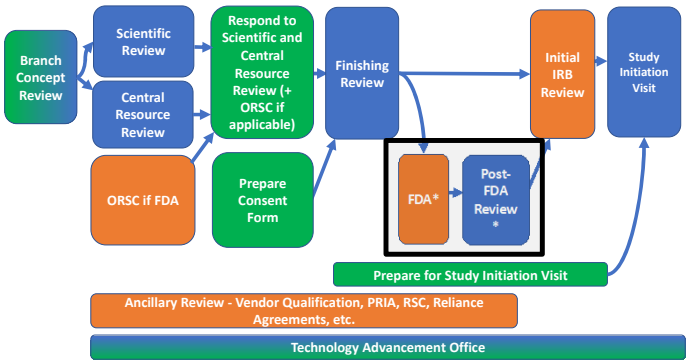
FDA Review & Finishing Review



***FDA review.** If your study involves an IND or IDE held by NIDDK or the Clinical Center, you will work with NIH ORSC to submit to FDA

***Post-FDA review.** If comments received from FDA require addressing, the PI should update the protocol and consent as appropriate and send back to finishing review.

Documents to be submitted for post-FDA finishing review include:

1. the clean protocol and consent that were submitted to FDA
2. tracked protocol and consent showing changes in response to FDA comments
3. a copy of the FDA comments and
4. a copy of the PI response to FDA comments.

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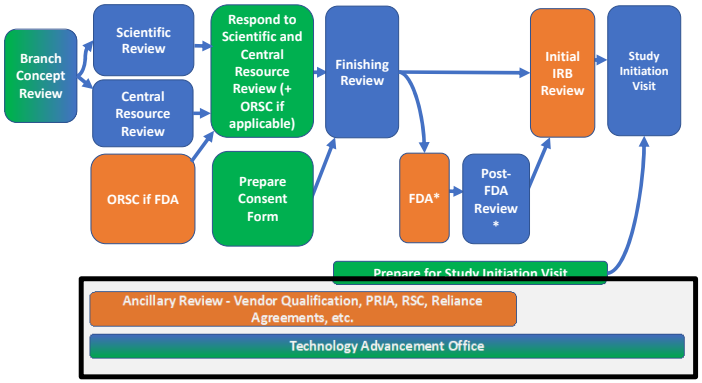
Ancillary Reviews



- Ancillary review submissions will be facilitated and timed by your protocol navigator in PROTECT and PQS

- May include:
  - DEC (financial conflict-of-interest)
  - Radiation Safety Committee
  - Prospective Protocol Resource Impact Assessment (PRIA)
  - Vendor verification process for study drugs

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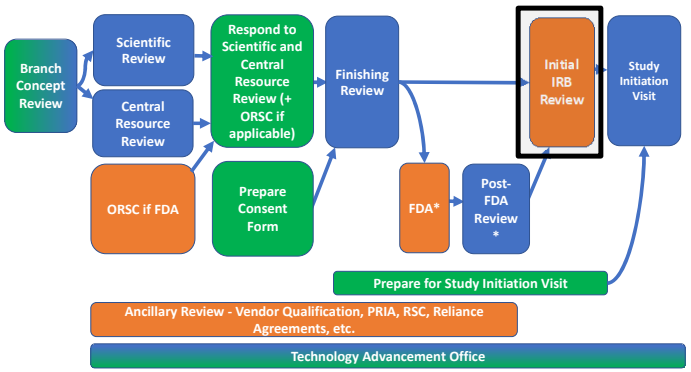
Initial IRB Review



- Facilitated by your protocol navigator in PROTECT
- Analysts at the IRBO will review the protocol
  - Common to request pre-review clarifications before IRB review
- When the IRB reviews the study, you may receive IRB approval, additional stipulations, or a deferral from the IRB.
  - If the outcome is deferral or includes stipulations, the IRB will re-review the study upon receipt of your response.

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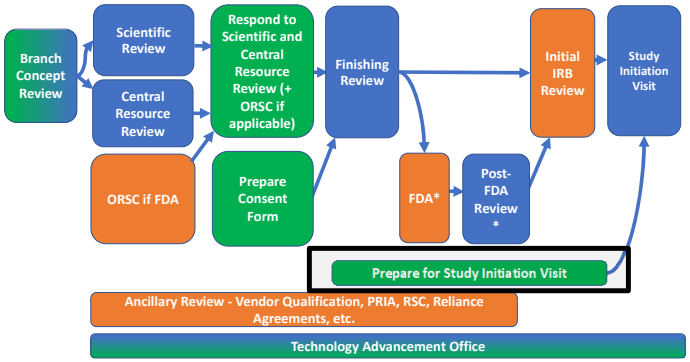
Study Activation Preparation



- NIDDK QA team will provide checklists to prepare for study activation process
  - You should begin process following resource review

- If an outside sponsor will monitor the study, NIDDK QA will perform a limited local study initiation review

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Study Activation Process

- While you're developing your protocol, you should prepare for your study activation review by building the tools and processes necessary to run the study, eg:
  - Regulatory binder
  - CRIS order sets
  - SOPs, worksheets, REDCap forms
  - Training for study team and unit teams

- At the end of study activation process, you should have everything ready to successfully conduct your study.

https://nih.sharepoint.com/sites/NIDDK-OfficeoftheClinicalDirector/SitePages/OCD-Site-Initiation-Visit-Process.aspx

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Resources & Support for Protocols in Development

- Protocol Writing Program & Protocol Navigators
- NIDDK Biostats
- NIDDK OCD:
  - QA/QI team
  - Clinical and Nursing Resources
  - Clinical Core Lab
  - Genetics/Genomics Considerations
  - Data Analytics & REDCap
- NIH ORSC Regulatory Support

Contact information, process information, and documents available at:

https://nih.sharepoint.com/sites/NIDDK-OfficeoftheClinicalDirector/SitePages/OCD-Protocol-Development-Process.aspx

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