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SCHOOL of MEDICINE

The JHM OHSR Compliance Monitoring Program Educational Seminar Series

Sponsor-Investigators (Investigational New Drug (IND)/Investigational Device Exemption (IDE) Holders) Institutional Requirements

09 November 2022

Speakers

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About You

Objectives

- Define: *Investigational New Drug* and *Investigational Device Exemption*
- Review responsibilities of Sponsor, Investigator, and Sponsor-Investigator, and need for Institutional IND/IDE Policy
- Provide an Overview of the IND/IDE Policy
- Introduce the IND/IDE Regulatory Program
- Summarize Johns Hopkins University “JHU” Investigator-held IND/IDE Review Procedures
- Post-approval Support from the Compliance Monitoring Program

Investigational New Drug (IND)

An IND is a drug that has **not** been approved for general use by the Food and Drug Administration but is under investigation in clinical trials regarding its safety and effectiveness first by clinical investigators using patients who have given informed consent to participate

Investigational New Drug (IND)

Title 21 United States Code (USC) Controlled Substances Act:

- Manufacture
- Importation
- Possession
- Use
- **Distribution**

Current Federal law requires that a drug be the subject of an **approved marketing application** before it is transported or distributed across state lines

The IND provides **exemption** from this requirement from FDA

Investigational Device Exemption (IDE)

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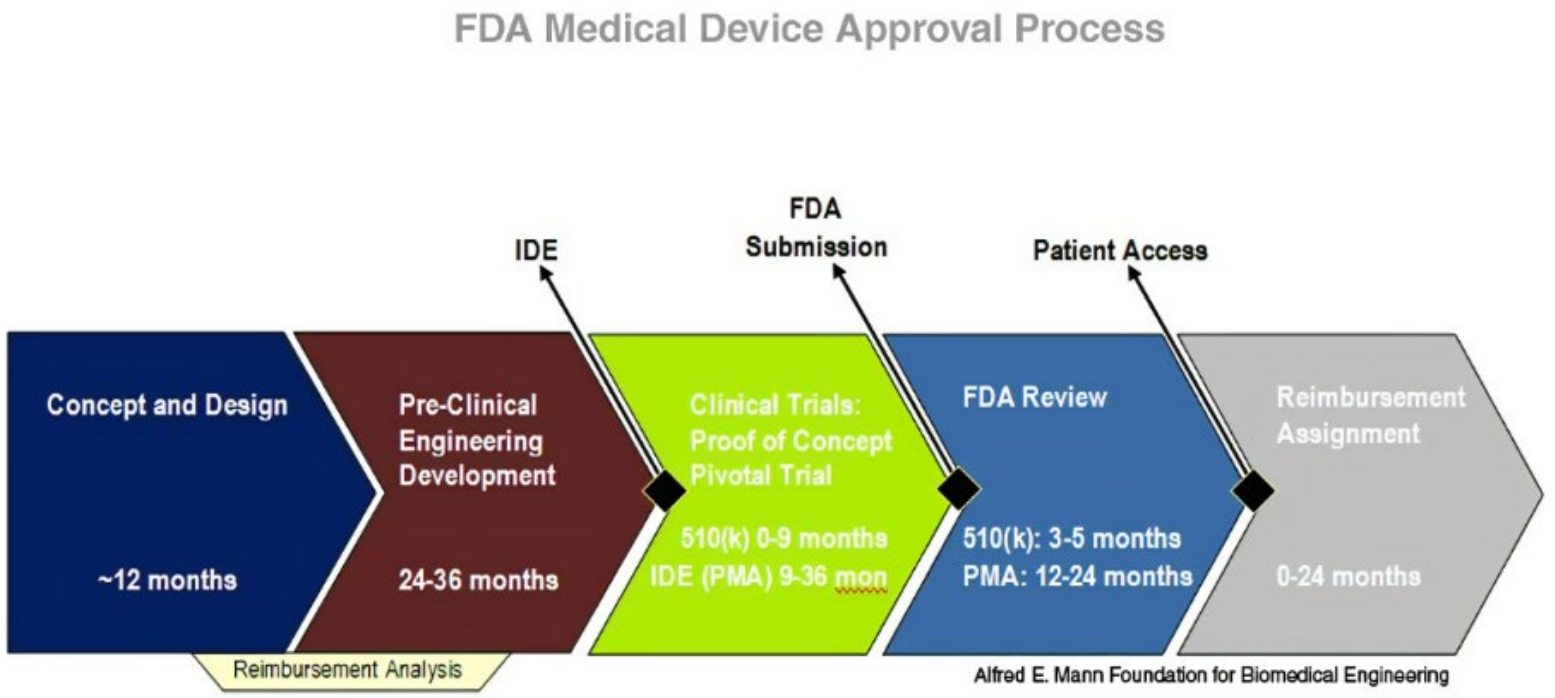
An IDE allows a medical device that has not received marketing clearance or approval to be shipped for use in a clinical study without complying with other regulations of the Federal Food, Drug and Cosmetic Act

All investigational devices fall under one of the following categories:

- Significant Risk (SR);
- Nonsignificant Risk (NSR); or
- IDE Exempt



Sponsor-Investigator Responsibilities

IND(s): 21 CFR Part 312 Subpart D

Subpart D - Responsibilities of Sponsors and Investigators

- § 312.50 - General responsibilities of sponsors.
- § 312.52 - Transfer of obligations to a contract research organization.
- § 312.53 - Selecting investigators and monitors.
- § 312.54 - Emergency research under 50.24 of this chapter.
- § 312.55 - Informing investigators.
- § 312.56 - Review of ongoing investigations.
- § 312.57 - Recordkeeping and record retention.
- § 312.58 - Inspection of sponsor's records and reports.
- § 312.59 - Disposition of unused supply of investigational drug.
- § 312.60 - General responsibilities of investigators.
- § 312.61 - Control of the investigational drug.
- § 312.62 - Investigator recordkeeping and record retention.
- § 312.64 - Investigator reports.
- § 312.66 - Assurance of IRB review.
- § 312.68 - Inspection of investigator's records and reports.
- § 312.69 - Handling of controlled substances.
- § 312.70 - Disqualification of a clinical investigator.

IDE(s): 21 CFR 812 Subpart C; E

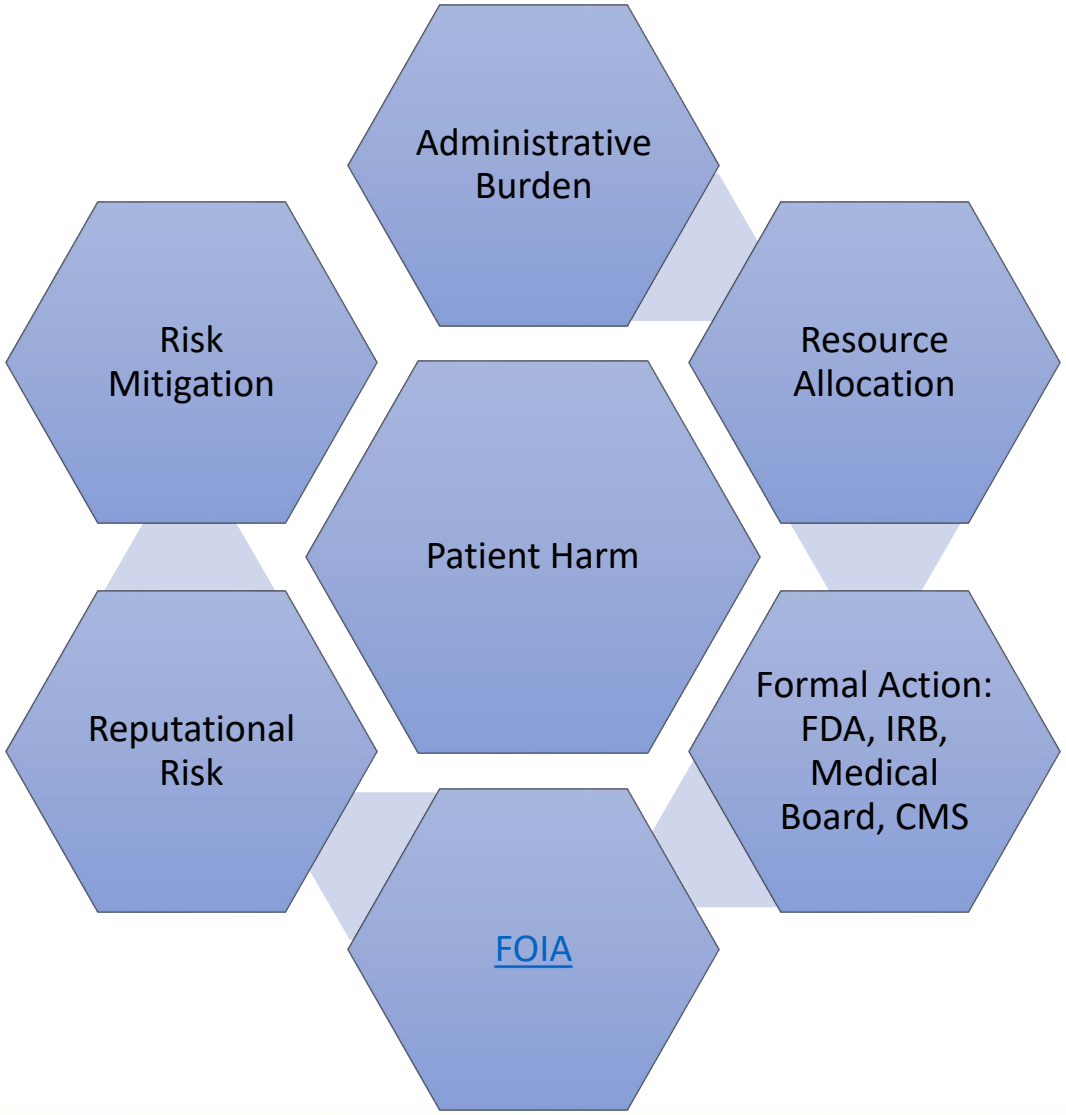
Subpart C - Responsibilities of Sponsors

- § 812.40 - General responsibilities of sponsors.
- § 812.42 - FDA and IRB approval.
- § 812.43 - Selecting investigators and monitors.
- § 812.45 - Informing investigators.
- § 812.46 - Monitoring investigations.
- § 812.47 - Emergency research under 50.24 of this chapter.

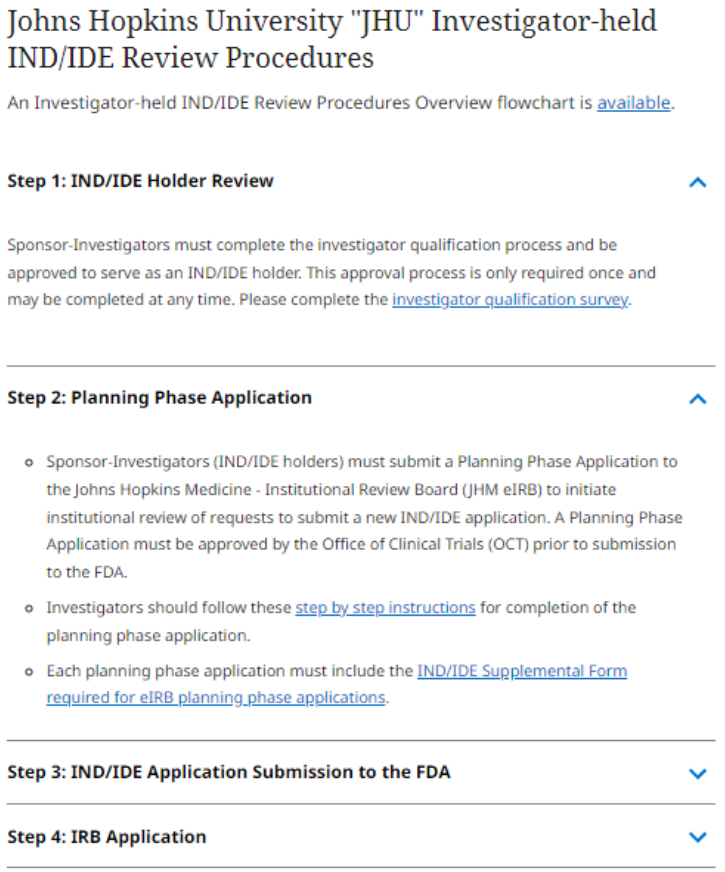
Subpart E - Responsibilities of Investigators

- § 812.100 - General responsibilities of investigators.
- § 812.110 - Specific responsibilities of investigators.
- § 812.119 - Disqualification of a clinical investigator.

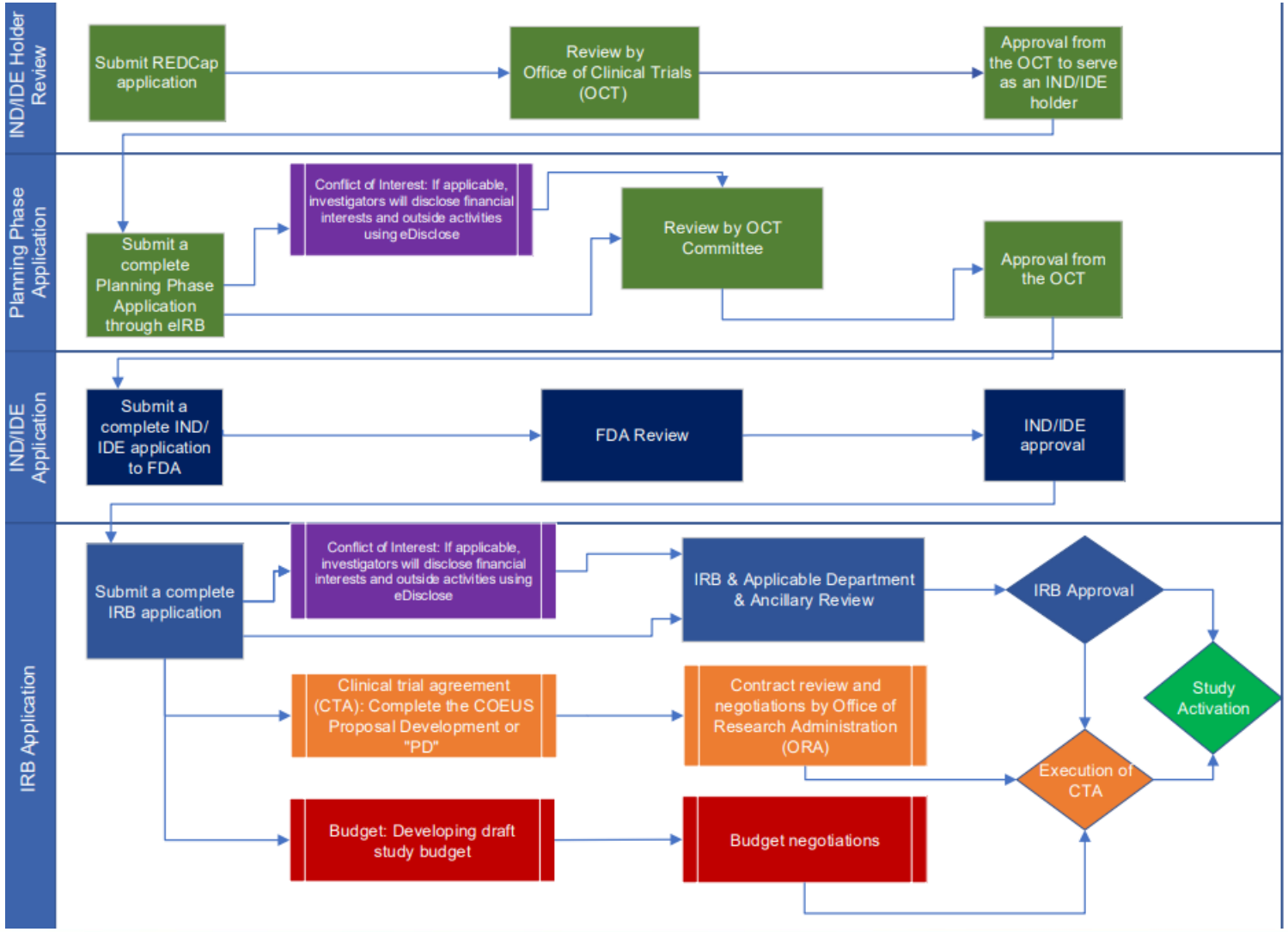
Why do we need an IND/IDE policy?



IND/IDE Policy – Implementation



JHU Investigator-held IND/IDE Review Procedures



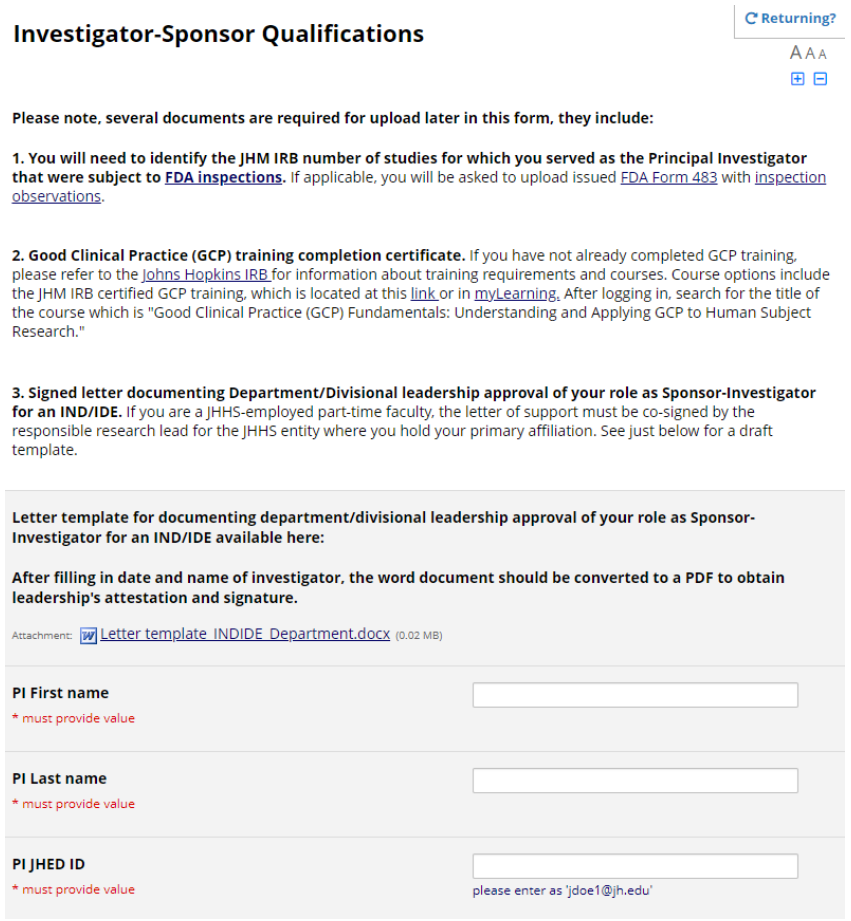
Step 1: IND/IDE Holder Qualification

Johns Hopkins University "JHU" Investigator-held IND/IDE Review Procedures

An Investigator-held IND/IDE Review Procedures Overview flowchart is available.

Step 1: IND/IDE Holder Review

Sponsor-Investigators must complete the investigator qualification process and be approved to serve as an IND/IDE holder. This approval process is only required once and may be completed at any time. Please complete the investigator qualification survey.



Investigator-Sponsor Qualifications

Returning?

A A A

Please note, several documents are required for upload later in this form, they include:

1. You will need to identify the JHM IRB number of studies for which you served as the Principal Investigator that were subject to FDA inspections. If applicable, you will be asked to upload issued FDA Form 483 with inspection observations.

2. Good Clinical Practice (GCP) training completion certificate. If you have not already completed GCP training, please refer to the Johns Hopkins IRB for information about training requirements and courses. Course options include the JHM IRB certified GCP training, which is located at this link or in myLearning. After logging in, search for the title of the course which is "Good Clinical Practice (GCP) Fundamentals: Understanding and Applying GCP to Human Subject Research."

3. Signed letter documenting Department/Divisional leadership approval of your role as Sponsor-Investigator for an IND/IDE. If you are a JHHS-employed part-time faculty, the letter of support must be co-signed by the responsible research lead for the JHHS entity where you hold your primary affiliation. See just below for a draft template.

Letter template for documenting department/divisional leadership approval of your role as Sponsor-Investigator for an IND/IDE available here:

After filling in date and name of investigator, the word document should be converted to a PDF to obtain leadership's attestation and signature.

Attachment: Letter template_INDIDE_Department.docx (0.02 MB)

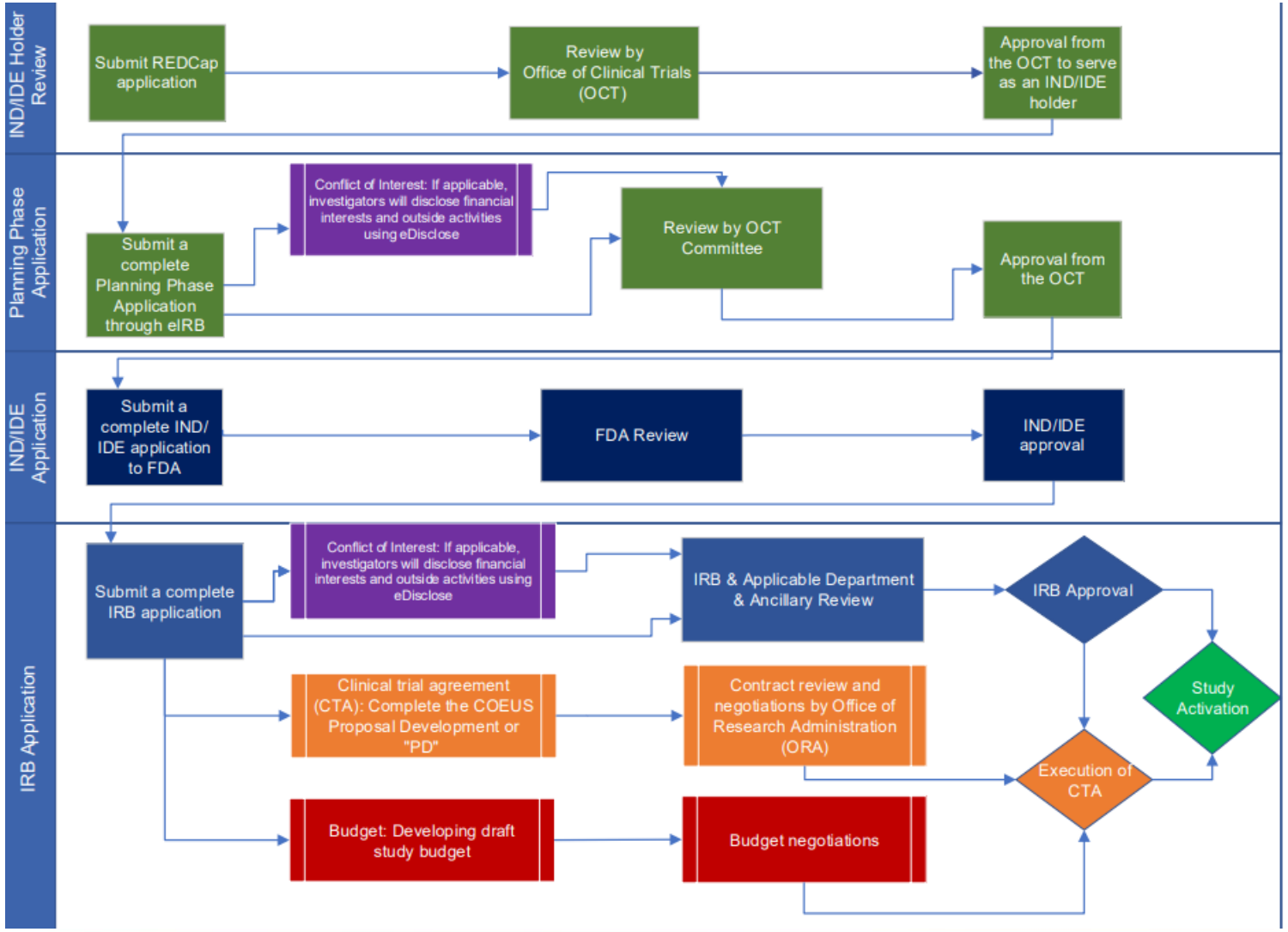
PI First name
* must provide value

PI Last name
* must provide value

PI JHED ID
* must provide value
please enter as 'jdoe1@jh.edu'

JHU Investigator-held IND/IDE Review Procedures

0-3 Calendar Days



Step 2: Planning Phase Application

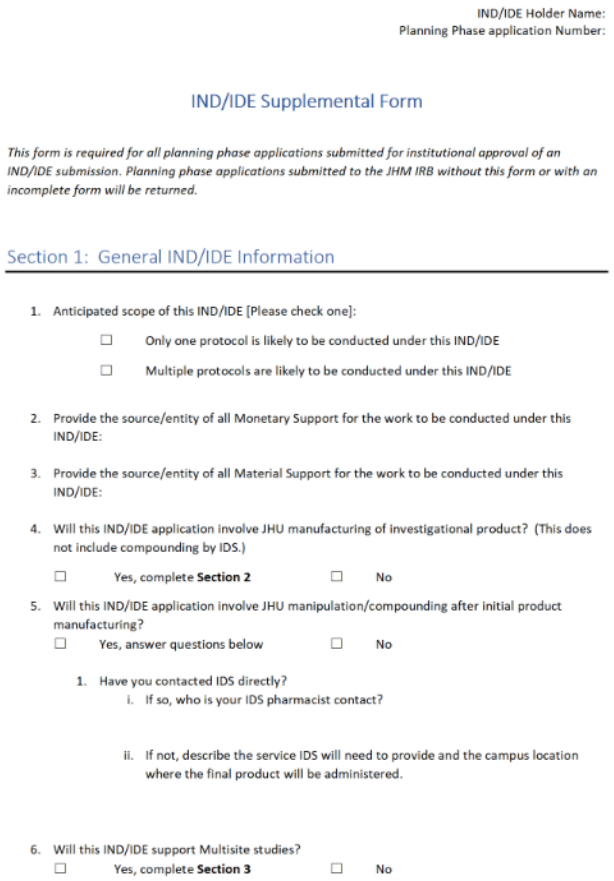
Johns Hopkins University "JHU" Investigator-held IND/IDE Review Procedures

An Investigator-held IND/IDE Review Procedures Overview flowchart is available.

Step 1: IND/IDE Holder Review

Step 2: Planning Phase Application

- Sponsor-Investigators (IND/IDE holders) must submit a Planning Phase Application to the Johns Hopkins Medicine - Institutional Review Board (JHM eIRB) to initiate institutional review of requests to submit a new IND/IDE application. A Planning Phase Application must be approved by the Office of Clinical Trials (OCT) prior to submission to the FDA.
- Investigators should follow these step by step instructions for completion of the planning phase application.
- Each planning phase application must include the IND/IDE Supplemental Form required for eIRB planning phase applications.



IND/IDE Holder Name:
Planning Phase application Number:

IND/IDE Supplemental Form

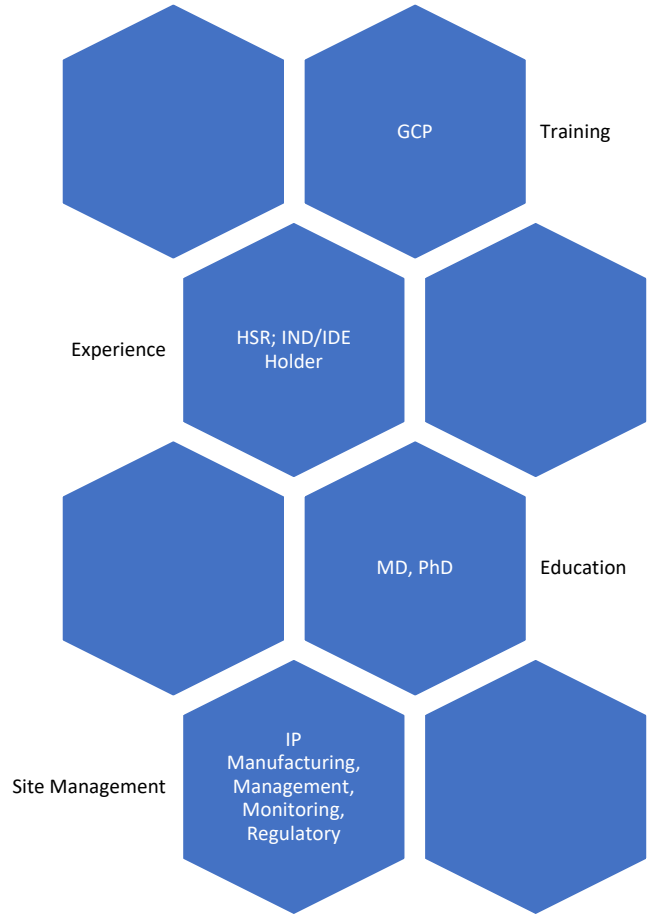
This form is required for all planning phase applications submitted for institutional approval of an IND/IDE submission. Planning phase applications submitted to the JHM IRB without this form or with an incomplete form will be returned.

Section 1: General IND/IDE Information

1. Anticipated scope of this IND/IDE [Please check one]:
   - ☐ Only one protocol is likely to be conducted under this IND/IDE
   - ☐ Multiple protocols are likely to be conducted under this IND/IDE
2. Provide the source/entity of all Monetary Support for the work to be conducted under this IND/IDE:
3. Provide the source/entity of all Material Support for the work to be conducted under this IND/IDE:
4. Will this IND/IDE application involve JHU manufacturing of investigational product? (This does not include compounding by IDS.)
   ☐ Yes, complete **Section 2** ☐ No
5. Will this IND/IDE application involve JHU manipulation/compounding after initial product manufacturing?
   ☐ Yes, answer questions below ☐ No
   1. Have you contacted IDS directly?
      i. If so, who is your IDS pharmacist contact?
      ii. If not, describe the service IDS will need to provide and the campus location where the final product will be administered.
6. Will this IND/IDE support Multisite studies?
   ☐ Yes, complete **Section 3** ☐ No

Sponsor-Investigator Suitability Assessment

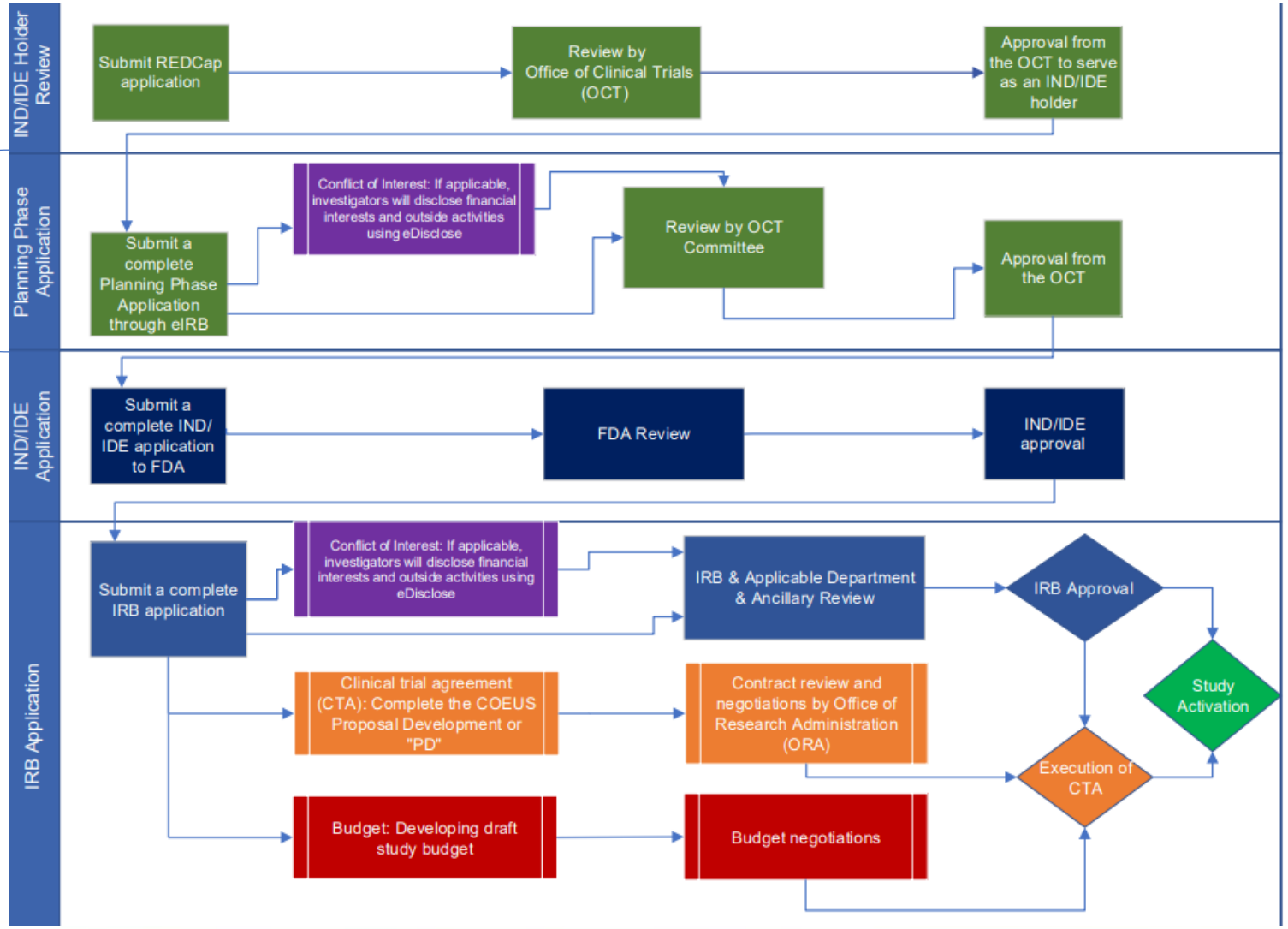
- ✓ The Sponsor-Investigator is appropriate, meets all applicable qualification requirements, and maintains sufficient resources to support the planned research
  - ✓ The Sponsor-Investigator of a more than minimal risk study (as determined by the IRB) may not have any of the interests outlined in Section III.B of University Policy GOV033 Conflict of Interest and Conflict of Commitment with respect to either the funder of the study, or the intellectual property represented by the drug, biologic, or device under investigation.
- ✓ Investigational Drug Management by Investigational Drug Services; Investigational Device Management using Plan Approved by OCT
- ✓ The study design and investigational plan meets FDA standards
  - ✓ Manufacturing Investigational Products
    - ✓ Pre-Qualification of JHU Manufacturing Facilities or Laboratories by Office of Clinical Trials
  - ✓ Monitoring
    - ✓ Pre-Qualification of Monitoring Programs by Office of Clinical Trials



Requests for pre-qualification may be submitted to IND_IDEprogram@jh.edu

JHU Investigator-held IND/IDE Review Procedures

35-45
Calendar Days



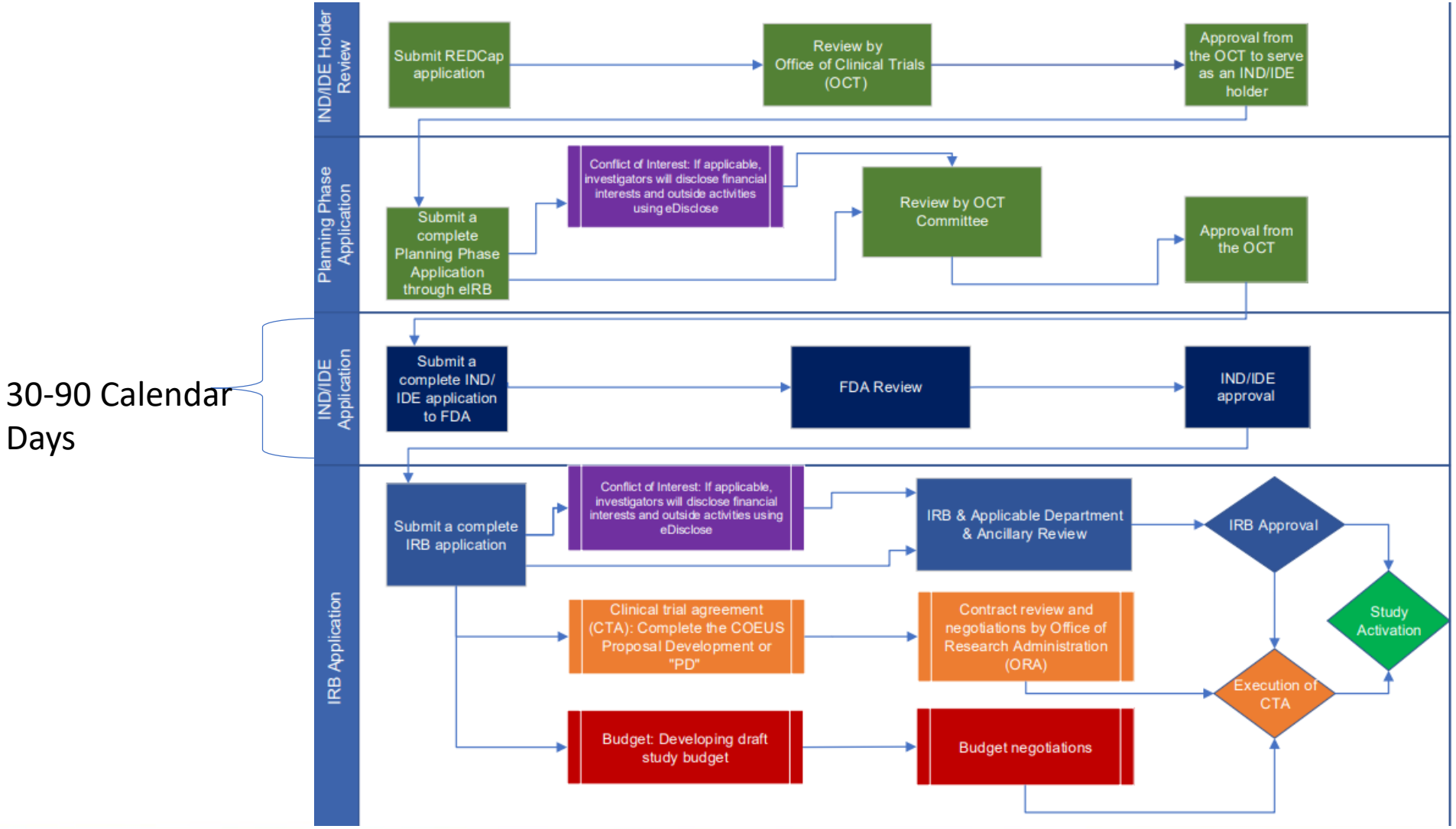
Step 3: IND/IDE Application Submission to FDA

- The Investigational New Drug (IND) Application | FDA contains information from the FDA to assist you in the IND application process. Once the IND is submitted, the sponsor must wait **30 calendar days** before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

- The IDE Approval Process | FDA contains information from the FDA to assist you in the IDE application process. Upon receipt of an IDE application, sponsors are notified via email of the date that the FDA received the original application and the IDE number assigned. An IDE application is considered approved 30 days after it has been received by the FDA, unless the FDA otherwise informs the sponsor via email prior to **30 calendar days** from the date of receipt, that the IDE is approved, approved with conditions, or disapproved. In cases of disapproval, a sponsor has the opportunity to respond to the deficiencies and/or to request a regulatory hearing under 21 CFR Part 16.

All IND/IDE applications must be filed with the OCT, and all FDA correspondence must be copied to the OCT: IND_IDEprogram@jh.edu

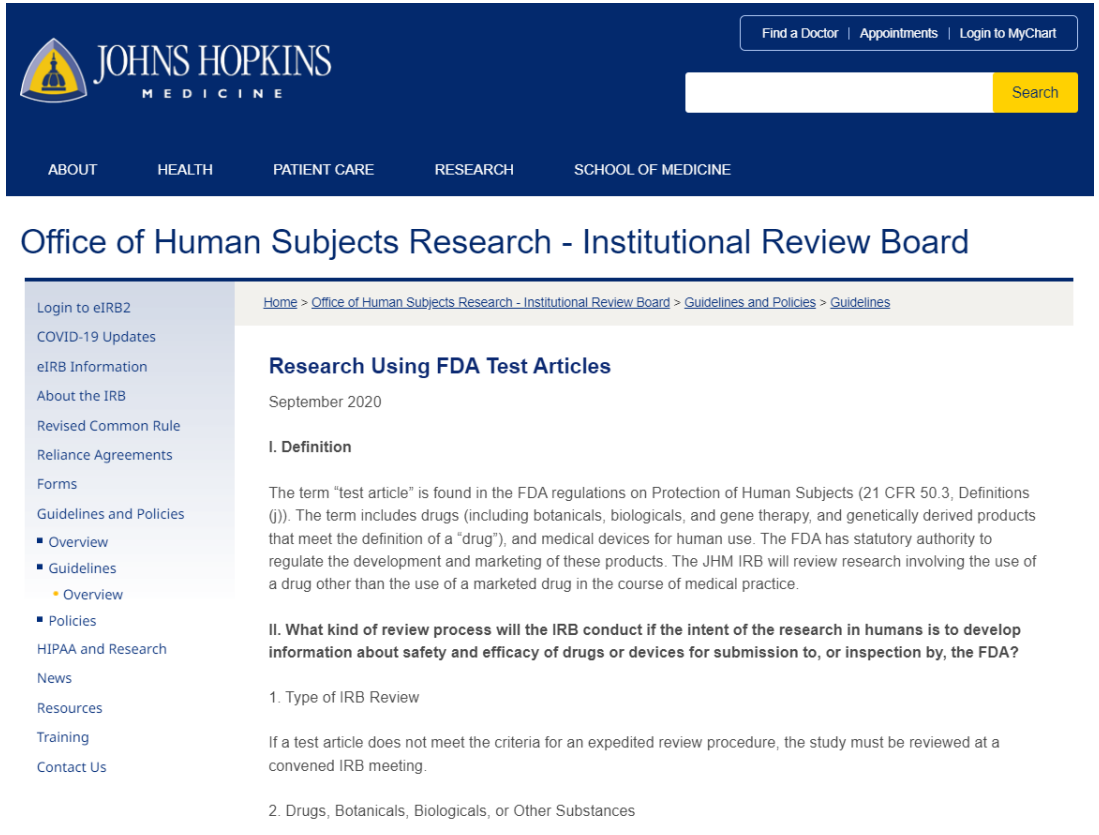
JHU Investigator-held IND/IDE Review Procedures



30-90 Calendar Days

Step 4: IRB Application

- In accordance with DHHS regulations 45 CFR Part 46 and FDA regulations CFR Title 21 Part 56, convened IRB review is required for the majority of new applications submitted to the JHM IRBs.
- A convened meeting is one at which a majority of members must be present, including a member whose primary concern is in a non-scientific area, before official actions may be taken.
- In order for the research application to be approved, it must receive approval of a majority of those members present at the meeting.
- The processing time for a protocol requiring convened review varies, depending upon how complete the application is at submission.

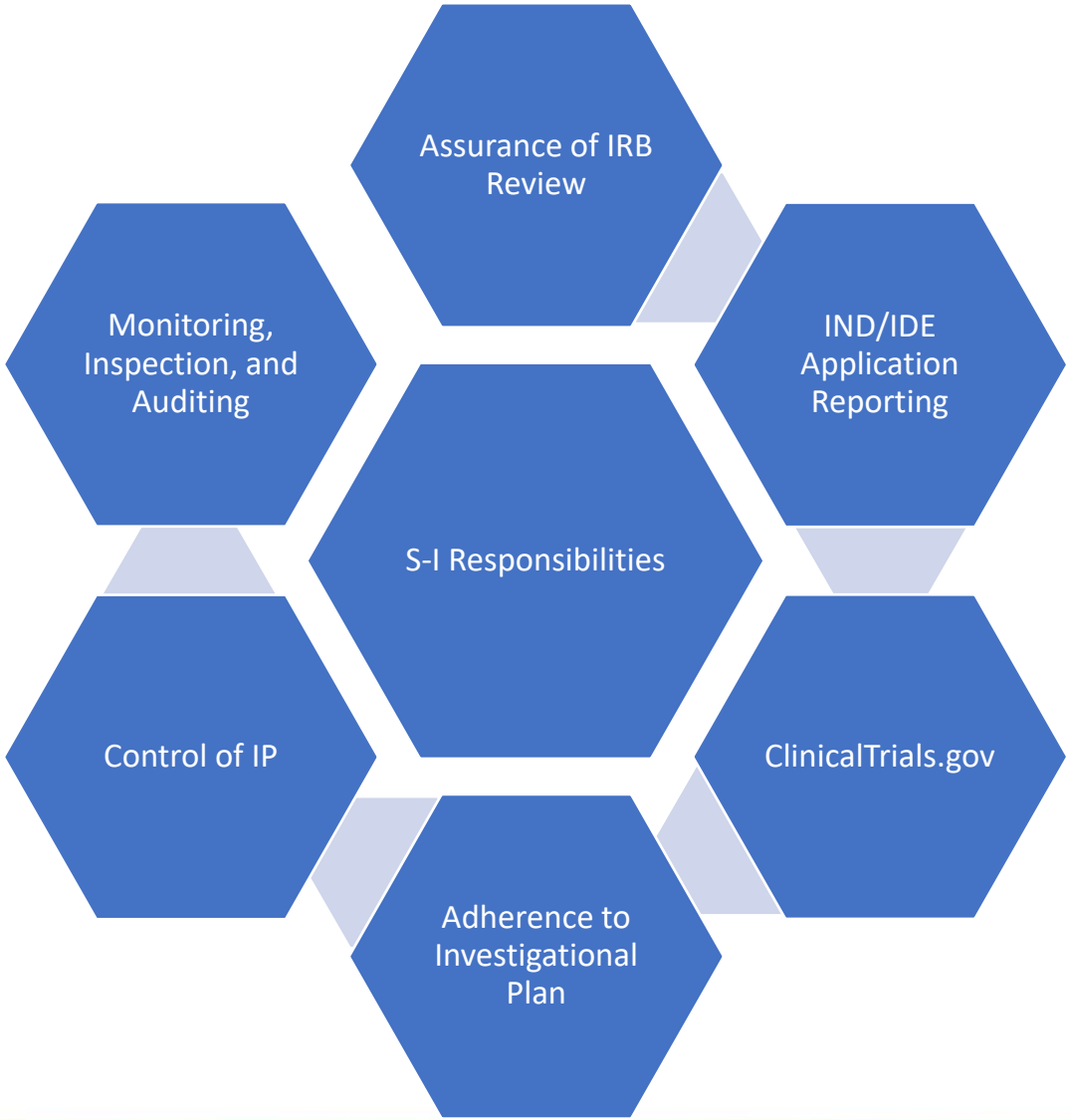


The JHM Office of Human Subjects Research - Institutional Review Board guidelines. Research Using FDA Test Articles

Post-Approval

Ensure the following are provided to the Office of Clinical Trials:

- ✓ **IND/IDE Submissions**
- ✓ **Associated FDA Correspondence**
- ✓ **Copies of Monitoring Reports**



Compliance Monitoring Program (CMP)

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Serve as a resource to Investigators (PI) and Research Personnel

Provide assistance to investigators at all phases of research

Examine convened IRB approved protocols for compliance with applicable regulations, institutional requirements, and “best-practices”

Post-Approval Monitoring efforts focus on:

- Priority Monitoring
- Directed Audits
- Pre-enrollment monitoring (for INDs and IDEs)

Monitoring Efforts for New Policy

- Pre-Enrollment Monitoring
  - Upon IRB approval the system notifies the CMP
  - Studies where JHU faculty holds the IND/IDE or a JHU faculty is using an IND/IDE held by JHU faculty
  - CMP staff contacts the PI to schedule a meeting
  - Meeting must occur before enrollment can begin

- In approximately 6 months – 1 year after the pre-enrollment review, a follow-up assessment will be conducted to confirm compliance and progress.

Pre-Enrollment Activities

- Review Investigator Responsibilities
  - 21 CFR 312 Subpart D - Responsibilities of Sponsors and Investigators
  - 21 CFR 812 Subpart C - Responsibilities of Sponsors
  - 21 CFR 812 Subpart E - Responsibilities of Investigators

Review of Sponsor-Investigator Responsibilities

- Per the applicable sections of the CFR for IND/IDE clinical trials
- Reporting Requirements (Safety)
  - IRB
  - FDA
  - JHU IND/IDE holder aka Sponsor (if applicable)
  - Other investigators (for a multi-center trial)
- Submission of changes to the protocol to FDA
  - Changes to the protocol can only be implemented after IRB approval
- FDA Annual Reports

Site Documents to be Reviewed

- Study May Proceed Notice from FDA
- FDA Form 1572 (INDs) or Statement of the Investigator (IDEs)
- CV's for staff listed on the 1572 or CV's for PI and sub-Investigators (IDE)
- Licenses as applicable
- Financial Disclosures
  - FDA Form 3454—No disclosures (can list all sub-investigators and sign)
  - FDA Form 3455– Fill out for each individual with a disclosure
- Certification of Registration of Clinical Trials
  - FDA Form 3674, including the NCT #
- Delegation of Authority Log with all IRB Approved Study Team members
- Adverse Event Log (template)
- Deviation Log (template)
- A summary of the IP accountability plan
- A summary of the monitoring plan, including the monitor's company and/or name (as applicable)

IND		IDE	Notes
Copy of IND 21 CFR 312 Sub-Part D given to the Sponsor-Investigator		Copy of IDE 21 CFR 812 Subparts C and E given to the Sponsor-Investigator	
IND 21 CFR 312 Sub-Part D instructions and applicable responsibilities reviewed with the sponsor-investigator • Reporting (annually within 60 days of approval date) • Record retention • Monitoring Plan • SAE's within 15 days; life threatening SAE's within 7 days		IDE 21 CFR 812 Subparts C and E instructions and applicable responsibilities reviewed with the sponsor-investigator • Selecting/Informing investigators • Reporting (at least annually) • Record retention • Monitoring plan • Unanticipated AE's within 10 working days • Emergency deviations within 5 working days • Current investigator list every 6 months	
FDA and IRB regulatory documents reviewed: • 1571/1572 • Licenses • CVs • CAP/CLIA • IRB approvals / correspondence • DSMB • Safety Monitoring • Drug labeling and IP accountability documentation • Delegation Log • 3674 • DEA approval		FDA and IRB regulatory documents reviewed: • Investigator Agreement • CV or statement of investigator experience • IRB approvals / correspondence • DSMB • Safety Monitoring • Device labeling and accountability documentation • Delegation Log	
A copy of the FDA Financial Disclosure Form 3454 an/or FDA Form 3455 was provided to the PI		A copy of the FDA Financial Disclosure Form 3454 an/or FDA Form 3455 was provided to the PI	
A monitoring plan is present, including the selection of a monitor FDA requirements under 312 ICF and participant files		A monitoring plan is present, including the selection of a monitor FDA requirements under 812 ICF and participant files	
Visit completion and enrollment authorization in eIRB notice generated		Visit completion and enrollment authorization in eIRB notice generated	
Remind the Investigator to inform the IRB if an FDA inspection notice is received. If a 483 is issued, the IRB requires a response to be submitted for its review.		Remind the Investigator to inform the IRB if an FDA inspection notice is received. If a 483 is issued, the IRB requires a response to be submitted for its review.	
Date of follow-up visit:		Date of follow-up visit:	

Common Findings

Outdated FDA Forms

Monitoring Plan – often confused with Data Safety Monitoring

Lab where Biospecimens are being processed and their listing on the 1572

Absent CAP/CLIA lab documents

Financial Disclosure Form-missing, incomplete or inaccurate

Delayed Clinicaltrials.gov registration and recording in eIRB

Delegation of Authority log inconsistencies

What happens if FDA issues a notice of inspection

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Notices come in writing (e.g. email)

Contact the CMP ASAP

The CMP can assist with prep for the inspection, time permitting

The CMP will also need to be present for the initial meeting with the Inspector to review credentials and the 482 (“Notice of Inspection”)

The CMP can attend later meetings with the inspector

Assists with any response to FDA

Conclusions

- Policy effective date June 1, 2022
- Support is available to assist Sponsors, Investigators, Sponsor/Investigators, and study teams in complying with associated requirements
- Engage the IND/IDE Regulatory Program and Compliance Monitoring Program early and often, as appropriate, to obtain support

Need Support?

- Regulatory Resources for INDs/IDEs, and information on Johns Hopkins University “JHU” Investigator-held IND/IDE Review Procedures

- For more information or questions, email the IND/IDE Regulatory Program: IND_IDEprogram@jh.edu

- Schedule a consultation

CMP Contact Information

- CMP Contact Information:
  - Fred Luthardt: fluthar1@jhmi.edu
  - Suzanna Roettger: sroettg1@jhmi.edu
  - Maggie Leathers: mleathe6@jhmi.edu
  - Katie Quinlan: kquinla4@jhmi.edu
  - Cierra Noel: cnoel2@jhmi.edu
- Feel free to call anytime…!