Investigational New Drug (IND) Binder Instructions

September 15, 2016

Instructions
This binder is available to help study sites achieve and maintain regulatory compliance when submitting to the Food and Drug Administration (FDA) and maintain an Investigational New Drug (IND) application.

Each section outlines the regulatory documentation requirements for Sponsor-Investigators and their research staff, tips and guidance, or best practice recommendations for organizational records. For your reference, the binder tabs feature hyperlinks to guidance and federal regulations.

Guidance for using the Regulatory Binder

- Tailor the binder to meet the needs of your protocol:
  - Organize and order the sections to facilitate ease of use and reference, e.g., by moving frequently used files referenced sections to the front of the binder.

- Keep the documentation in the binder current and up-to-date.

- Identify an individual(s) responsible for maintaining the binder. Ensure that this person will have access to correspondence (e.g. from FDA and/or clinical sites) and documentation that are received so they may update the binder in a timely manner.

- Store binder in a safe and secure location, but keep accessible to study staff at all times. If sections or contents within the binder (e.g. drug/device logs) are maintained electronically or stored elsewhere (e.g. research pharmacy), be sure there is a note-to-file referencing where the electronic sections are being maintained and by whom.

- Participant-specific documentation and information, e.g., signed consent forms, test results, and completed case report forms, as well as materials submitted to, and approved by, the IRB of record should be maintained separately in participant-specific binder/files and a regulatory binder. The Harvard Catalyst Regulatory Binder is an example of a resource that can be used for this purpose.

Sections included in Binder
Use the below list to ensure that the applicable sections are maintained. For questions, please contact the appropriate institutional support.

1. Pre-IND Submission
2. IND Submission
3. IND Maintenance
   a. Requirements - Amendments
b. Safety Reports  
c. Annual Reports  
4. Site Information  
5. IND Closure/Withdrawal
Pre-IND Submission

Requirements

☐ Maintain all pre-IND Correspondence with FDA and/or IRB.
☐ Obtain data/information related to previous human experience studies.
☐ Obtain data/information related to prior animal studies.
☐ Obtain data/information related to pharmacology/toxicology studies.
☐ Obtain data/information related to chemistry, manufacturing, and control.
☐ Maintain Investigator’s Brochure.

Tips

✓ Consider contacting the FDA, IRB, or Harvard Catalyst for a pre-IND consult if uncertain about the applicability of the IND
✓ Investigator’s Brochure, chemistry manufacturing and controls, pharmacology/toxicology, and previous human experience data may be provided by referencing to drug labeling or to letters of authorizations (cross reference letter from drug manufacturer/sponsor)

Guidance/Best Practice Recommendation

Investigational New Drug Applications (INDs) – Determining Whether Human Research Studies Can Be Conducted Without an IND

IND Exemptions - 21 CFR Part 312.2(b)(1)

Sponsor-Investigator Responsibilities – Regulation and Clinical Trials

Investigator Initiated Investigational New Drug (IND) Applications
**IND Submission**

**Requirements**
- Maintain all correspondence with FDA related to IND submission.
- Maintain all correspondence, including approval letter, with IRB.
- Maintain submitted IND application (including Cover Letter 1571, Form FDA 1572, table of contents, introductory statement, investigational plan, Investigator’s Brochure, protocols, chemistry and manufacturing controls, pharmacology/toxicology, previous human experience, additional information).
- Form FDA 3674: Certification of compliance for clinical trial registration (instructions available [here](#))
- Form FDA 3454 or Form FDA 3455: Certification of Financial Interests (these links are provided below)

**Tips**
- FDA requires original and two additional paper copies of IND application (paginated)
- After the FDA receives the IND, an IND Acknowledgement Letter will be sent to the Sponsor–Investigator
- This letter contains important information such as the name of the project FDA manager (point person for questions about the IND), the IND Number, and official FDA date of receipt.
- **Important:** The trial may not be initiated until 30 calendar days after the official FDA receipt date listed on the letter. If the FDA has safety concerns, FDA will contact the Sponsor-Investigators within 30 days of receipt of the letter.
- The FDA could place the study on clinical hold until any concerns are resolved. Sponsor-Investigator should respond to FDA as soon as possible. The study may not commence until clinical hold is lifted.
- In all cases, IRB approval must be obtained before a trial can commence.

**Guidance/Best Practice Recommendations**
- [Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators](#) (Draft guidance)
- Content of an IND ([21 CFR 312.23](#))
- [Investigator Checklist for IND Submissions](#)
- [Form 1571 Instructions](#)
- [Form 1572 Instructions](#)
IND Maintenance

Requirements - Amendments

- Report changes to protocol (includes brief summaries of differences between new and revised protocol amendments) that significantly affects the safety of subjects, scope of the investigation, or quality of the study.

- Report addition of new investigators (if multiple investigators are expected, the Sponsor can lump together and submit in 30-day intervals)

- Report new addition of new protocol to the IND

- Report informational amendments (e.g. new technical information or discontinuation of a study at clinical sites)

Tips

- Changes to protocol still require IRB approval in addition to FDA approval. Maintain copies of all protocol versions
- Amendment must be submitted to the IND file with a Form FDA 1571 numbered sequentially
- A cover letter should be included with submission of all amendments

Federal Regulations/Good Clinical Practice

Investigators Responsibilities (Subpart D of 21 CFR 312)

Protocol Amendments (21 CFR 312.30)

Information Amendments (21 CFR 312.31)
IND Maintenance

Requirements – Safety Reports

☐ Report any adverse experience associated with the use of the drug that was both serious and unexpected

Tips

✓ Report fatal or life-threatening conditions within seven days to FDA. Other conditions can be reported within 15 days of when the investigator learns about these conditions.
✓ Report events per your IRB reporting requirements
✓ Use FDA Medwatch form 3500 (voluntary reporting for healthcare professions) or 3500A (mandatory reporting for IND holders/manufacturers) to facilitate reporting to FDA. Foreign events are submitted via CIOMS form (Council for International Organizations of Medical Sciences).
✓ Reports must be submitted with a Form FDA 1571 numbered sequentially.

Guidance / Best Practice Recommendation

IND Safety reporting guidance (Safety Reporting Requirements for INDs and BA/BE Studies)

Safety Reports (21 CFR 312.32)
IND Maintenance

Requirements – Annual Reports
☐ Submit annual reports to the FDA within 60 days of IND effective date

Tips
✓ Content of annual reports should contain information related to the study, summary of safety information, general investigational plan, Investigator’s Brochure, protocol modifications, foreign marketing developments, and outstanding business
✓ Report must be submitted with a Form FDA 1571 numbered sequentially

Guidance / Best Practice Recommendation
- IND Annual Reports (312.23(a)(3)(iv))
  Annual IND Report Template
Requirements
- Maintain current investigator’s CVs, licensure(s), financial disclosure(s)
- Maintain a 1572 listing all investigators at the site(s)
- Maintain documentation of monitoring (from each site) – e.g. monitoring reports and logs

Tips
- Submit updates to FDA within 30 days of when new sites are enrolled
- Ensure site investigators notify local IRB of updates/changes to study staff
- Report must be submitted with a Form FDA 1571 numbered sequentially

Guidance/ Best Practice Recommendations
Financial Disclosures (21 CFR Part 54)
- Certification: Special Interests and Arrangements of Clinical Investigators
- Disclosure: Financial Interests and Arrangements of Clinical Investigators

GCP 4.1.1

Oversight of Clinical Investigations – A Risk Based Approach to Monitoring
IND Closure/Withdrawal

Requirements
- Obtain IRB approval for closure or withdrawal of IND
- Maintain correspondence to/from the FDA regarding request for closure/withdrawal

Tips
- If IND is inactive for more than 5 years, the FDA may terminate the IND. An Inactive IND may be reactivated via a Protocol Amendment.
- The FDA may terminate an IND at any time due to safety issues or deficiencies in the IND, or conduct an investigation
- Closure documentation must be submitted to IND file with a form FDA 1571 numbered sequentially

Guidance / Best Practice Recommendation
Inactive Status of IND (21 CFR 312.45)