Investigational New Drug Development Steps for CRCs
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Learning Objectives

- Define an IND, types of INDs, and review related terms.
- Identify when you may need to apply for an IND or request an IND-exemption from the IRB.
- Review each of the steps in preparing an IND submission.
- Review the process for maintaining an existing IND including protocol amendments, safety reports and annual reports.
- Identify your resources in the IND process.
What is an IND?

- IND stands for Investigational New Drug
- An IND application is a request to the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans who are enrolled in a clinical trial.
- IND categories are: commercial or research (non-commercial, academic)
- Other key terms
  - IDE – Investigational Device Exemption
  - Combination products (drug/device combination)
    - Example: a drug eluding stent -> IND or IDE?
- Use of an IND always requires UCSF IRB Approval unless it is a rare case of Emergency Use.
Sequence of IND Study Steps

(1) Develop Protocol and Determine IND needs
- PI develops the Study Protocol.
- Determine if you need to apply for an IND, or need an IND-exemption.
- Hold a pre-IND consultation meeting if needed (optional).

(2) Apply for IRB and IND
- Complete and submit both applications concurrently.

(3) Within 30-days of IND submission
- FDA will send an acknowledgement letter detailing:
  - Date acknowledged & 30-day date study may proceed (if no clinical hold)
  - *If you don’t hear from FDA, email them to follow up.

(4) 30+ Days from IND Date of Acknowledgement
- The IND is effective!
- Submit Protocol Amendments & Safety Reports as needed.
- Submit Annual Report within 60 dates of anniversary.
How do you know you need one?

- If your Principal Investigator is:
  - Proposing the study of an **unapproved drug** (not currently commercially available).
  - Proposing the study of an **approved drug** for a **new indication**.
  - Proposing the study of an **approved drug** for **new advertising**.
  - Proposing the study of an **approved drug** in a **new patient population**.
  - Proposing the study of an **approved drug** with a **new route of administration or dosage**.

- Use the IND Decision Worksheet
- Hold pre-IND Consultation meeting
## Types of INDs

<table>
<thead>
<tr>
<th>Investigator Initiated IND (aka: Investigator-Sponsor)</th>
<th>Industry Sponsored IND (aka: Commercial INDs)</th>
<th>Expanded Access IND (aka: Compassionate Use)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submitted by the individual who initiates and conducts the investigation and under whose immediate direction the investigational drug is administered.</td>
<td>Submitted by a pharmaceutical company who sponsors the research that will occur with the IND. The Sponsor does not actually conduct the investigation.</td>
<td>Allows certain individuals not enrolled in clinical trials to obtain expanded access to investigational drugs/agents if there is:</td>
</tr>
<tr>
<td>The PI holds the IND.</td>
<td>The Sponsor holds the IND.</td>
<td>a serious or immediately life-threatening disease or condition</td>
</tr>
<tr>
<td>Most of the time, this is non-industry funded sources (ex: NIH).</td>
<td>This is all industry funded.</td>
<td>the patient benefit justifies the potential risks of the treatment</td>
</tr>
<tr>
<td>This is a Research IND.</td>
<td>This is a Commercial IND.</td>
<td>the use will not interfere with clinical investigations that could support marketing approval</td>
</tr>
</tbody>
</table>
Expanded Access INDs

- **Individual Patient Emergency Use**
  - Allows use of an experimental drug in an emergency situation for one patient when there is not adequate time to submit an IND.

- **Intermediate Size Patient Populations**
  - More than one patient, but less than a traditional IND. There is preliminary clinical evidence of effectiveness of the drug to make the expanded access use a reasonable therapeutic option in the anticipated patient populations.

- **Treatment**
  - Submitted for experimental drugs that show promise in clinical settings for serious or life threatening conditions, while FDA is reviewing.
IND Exemptions

- **AKA: IND Waiver; you are exempt from submitting IND application**

- **Exemption scenario:** Significant use of the drug “off-label” for a particular indication, and this is well-documented in literature.

- **Work with the IRB first to gain an exemption**
  - Submit an exemption request to the FDA if the IRB requires it.

<table>
<thead>
<tr>
<th>Explain</th>
<th>Attach</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the iRIS “Drug” Section, explain why an exemption is appropriate.</td>
<td>Always attached your IND Decision Worksheet in “Other IRB Documents”</td>
</tr>
<tr>
<td>Explain why you are not adding undue, additional risk.</td>
<td></td>
</tr>
<tr>
<td>Reason is: Significant off-label use</td>
<td>A piece of literature documenting significant use of the drug off-label.</td>
</tr>
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Preparing to Submit an IND

- You will need the following materials:
  - IND Cover Letter
  - IND Application
  - IND Protocol
  - Investigational New Drug - Form 1571
  - Statement of Investigator - Form 1572
  - Conflict of Interest – Form 3454 OR Form 3455
  - Certification Form 3674

- As a CRC, you likely will be asked to help draft all of these sections of the IND submission.
IND Cover Letter

- The first piece of information seen by the FDA
- Expresses the intent of the investigator to request FDA review and briefly describes the proposed research

Helpful Tips:
- Keep it short (1-2 pages)
- Make sure the date of the Cover Letter matches the date on the FDA Form 1571
- Your serial number will start as “000”. Any subsequent correspondence will be (001, 002, 003, and so on)
- If you’ve had a pre-IND meeting with the FDA, note this in the Cover Letter

Use template provided on the HUB
IND Application

- Prepared by the Investigator. CRCs may be asked to compile or draft necessary information.
- Information is compiled on the following areas:
  - Animal Pharmacology & Toxicology Studies (aka: preclinical data)
  - Manufacturing Information
    - Drug Master File (DMF)
    - Letter of Authorization (LOA)
  - Clinical Protocol & Investigator Brochure
- Use the template provided on the HUB
IND Protocol

- A completed protocol is required within the IND Application.
- This is different from your study protocol, but there are some overlapping sections.

Helpful Tips
- Begin with the protocol synopsis
- Keep a list of all of your references and copies of all papers listed
- Make sure safety monitoring based on known safety risks is included.

- Use the protocol template provided on the HUB
Investigational New Drug - Form 1571

- The 1571 is required to:
  1) obtain agreement from the sponsor (or sponsor-investigator) to conduct research according to all appropriate FDA regulations
  2) serve as a cover sheet for all submissions to the FDA on behalf of a particular IND
Investigational New Drug - Form 1571

- **Required contents:**
  - Contact information & mailing address of the Investigator/Sponsor
  - IND number, if it has been issued
  - Serial number
  - The name(s) of the drug/biologic and the indication being studied
  - The contents of the submission
  - Name and title of the individuals responsible for monitoring the study and reviewing safety data.
Statement of Investigator - Form 1572

- The 1572 is required because:

  • It is a signed agreement from the Investigator that he/she will conduct the research in compliance with FDA regulations.

  • It collects all the clinical site and investigator information needed by the sponsor (or sponsor-investigator) to assure the FDA that all investigators have the experience and background needed to conduct the trial.
Statement of Investigator - Form 1572

- **Required Contents:**
  
  - A current CV or statement of qualifications of the investigator(s) listed on the 1572. It does not need to be signed.
  
  - Name and address of the location where the clinical investigation will be conducted, the clinical laboratories that will be used, and the IRB reviewing the study.
  
  - Names of the sub-investigators at the site.
Conflict of Interests Forms 3454 or 3455

- You must submit financial disclosures for the PI.
- Regulations are intended to ensure that financial interests and arrangements of clinical investigators that could affect the reliability of data submitted to FDA are identified and disclosed by the applicant.

- **3454 - Certification**: Financial Interests and Arrangements of Clinical Investigators
  - For those investigators certifying that those investigators hold none of the identifiable disclosable financial arrangements.

- **3455 – Disclosure**: Financial Interests and Arrangements of Clinical Investigators
  - Disclosing the financial interests and arrangements and steps taken to minimize the potential for bias.
Certificate of Compliance Form 3674

- The 3674 is required because:
  - It is a signed statement from the sponsor/investigator that they will comply with clinicaltrials.gov requirements concerning their investigation.
  - If clinical trial is funded through the NIH, it is a Federal requirement to register it on clinicaltrials.gov.

- NOTE: You also will need to submit to clinicaltrials.gov (requirement for publishing)
Certification of Compliance Form 3674

- **Helpful Tips**
  
  - **Box A**
    - Check only if there **is not** a clinical investigation covered in the IND submission.
    - This is not common.
  
  - **Box B**
    - In regards to whether the trial is an applicable trial.
  
  - **Box C**
    - **This is the most common**.
    - Check if there is a clinical investigation **and** requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act **do** apply.
Paper Trail & Documentation

- **Study Team**
  - Materials go to the Center for Drug Evaluation and Research (CDER) at the FDA.
  - Send 3 total (1 original with wet signature and 2 copies) of the entire submission.
  - File a copy in your Regulatory Binder.
  - Send application packet via overnight courier.
  - Save shipping receipt to confirm delivery.

- Use Checklist on the Hub when compiling all materials
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PI develops the Study Protocol.

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*If you don’t hear from FDA, email them to follow up.

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Submit Protocol Amendments & Safety Reports as needed.

Submit Annual Report within 60 dates of anniversary.
Communication from the FDA

- Within 30-days of submission
  - FDA sends an acknowledgement letter providing an IND number.
  - FDA will notify you if there is a clinical hold or if they have concerns.
- IND goes into effect 30 days after acknowledgement
  - If you don’t hear anything, this likely means it is safe to proceed, but follow up in an email so you can document it.
- The FDA **does not** send you an approval letter.
  - They may send you a letter saying your study is **safe to proceed**.
IND Maintenance

- Once the IND goes into effect, the Investigator is responsible to maintain it.
- Work with your PI to assist with the 3 reporting responsibilities
  1. Amendments
  2. Safety Reports
  3. Annual Report
- If you are the coordinating center for a trial, monitoring and reporting is required of all of the sites.
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Amendments

- Two categories of amendments: Protocol & Information
- Protocol Amendments
  - New Protocols
  - Changes to existing protocols
  - New Investigator
- Information Amendment
  - New toxicology, chemistry, or other technical information.
  - If clinical investigation is discontinued.
**Protocol Amendments**

<table>
<thead>
<tr>
<th>New Protocol</th>
<th>Change in Protocol</th>
<th>New Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adding another study protocol to the IND.</td>
<td>Increase in drug dosage or duration of exposure.</td>
<td>Adding a new investigator to the IND.</td>
</tr>
<tr>
<td></td>
<td>Increase in # of participants.</td>
<td>Adding a new site to the IND.</td>
</tr>
<tr>
<td></td>
<td>Design changes (ex: adding or dropping a control group).</td>
<td>Transferring the IND obligations.</td>
</tr>
<tr>
<td></td>
<td>Adding a new test or procedure.</td>
<td></td>
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<tr>
<td></td>
<td>Dropping a test that monitors safety.</td>
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</tbody>
</table>
Submitting Protocol Amendments

- Submit amendment **before implementing** the changes.
- Bundle as much as possible.
- FDA does not want to receive more than 1 amendment within 30-days.

- You can submit to the IRB & FDA in the order of your choosing
  - If you already have approval from the IRB, send in the approval letter.
Protocol Amendment Materials

- IND Protocol Amendment Form
- IND Cover Letter
- FDA Form 1571
- If new investigator or site also submit
  - Form 1572 & Curriculum Vitae (CV) of new PI
  - COI Forms 3454 or 34551
- Send one original with wet signature & 2-copies

See Protocol Amendment Template on the HUB.
Submitting Information Amendment

- IND Cover Letter
- FDA Form 1571
- Statement of the nature and purpose of Information Amendment
- Organized presentation of information/data to be reviewed
- A request for comment, if Sponsor wants the FDA to comment.
Safety Reports

• Safety Reports Needed when:
  • There is an adverse event which is
    – Associated with the use of the drug AND
    – Both Serious and Unexpected
  • New preclinical tests show significant risk for humans

• Remember that reporting to the IRB is also required. Follow IRB required reporting timelines.
How to send in a Safety Report

• Send within 15 calendar days of notification of the event, the following:
  – The FDA MEDWatch 3500A Form
  – An IND Safety Report Cover Letter

• Special Cases:
  – If an adverse event is an unexpected fatal or life-threatening experience you must
    ▪ Place a telephone call or facsimile transmitting within 7 calendar days
    ▪ Follow up with the safety report within 8 calendar days
Annual Report

- Due to the FDA within 60 days of the anniversary of the date the IND went into effect.
  - The Annual Report contains 7-Sections
    - Individual study information
    - Summary of clinical & non-clinical information
    - Update to general investigational plan
    - Update to Investigator’s Brochure
    - Protocol updates
    - Foreign market updates
    - Log of outstanding business
  - Also submit
    - Cover Letter
    - Form 1571
  - Download the report template from the HUB.
Your Resources

- **Contacts**
  - Regulatory Support Office (Melanie Hassel)
    https://compliance.ucsf.edu/fda-support

- **Websites**
  - UCSF Clinical Resource HUB: http://hub.ucsf.edu/ind-development-process
  - UCSF IRB: http://irb.ucsf.edu/investigational-new-drugs-and-biologics
FAQs

- Can a non-medical doctor Principal Investigator (i.e. PhD) submit an IND or IDE?
  - Yes, but must have a medical monitor as part of study personnel.

- Do I need to submit an IND for a placebo drug?
  - No

- What if I add a new questionnaire? Do I need to submit an amendment?
  - Most likely not, because it does not apply to any of the components of the IND. Explain during annual report instead.
Questions?
Please take the course evaluation!

- We want to hear your thoughts about this course!
- A link to an evaluation survey will be coming to your email. Please complete it and let us know your thoughts.