Responsibilities of IND Sponsor-Investigators

AGENDA

1. INVESTIGATIONAL NEW DRUG (IND) APPLICATION PROCESS
   - WHAT IS AN IND?
   - APPLICABLE REGULATIONS
   - SPONSOR AND INVESTIGATOR RESPONSIBILITIES
   - IND APPLICATION SECTIONS
   - IND “MAINTENANCE”
   - COMMON MISTAKES/VIOLATIONS

2. MICHR IND/IDE ASSISTANCE PROGRAM (MIAP) OVERVIEW

3. CLOSING THOUGHTS and Q & A
What is an IND?

• The United States FDA Investigational New Drug (IND) program is the means by which a pharmaceutical company (or other entity) obtains permission to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved.

• The FDA reviews the IND application for safety to assure that research subjects will not be subjected to unreasonable risk. If the application is approved, the candidate drug usually enters a Phase 1 clinical trial.
What is an IND? (continued)

• The IND is not an application for marketing approval. Rather, it is a request for an exemption from the Federal statute that prohibits an unapproved drug from being shipped in interstate commerce.

• The IND is the means through which the sponsor technically obtains this exemption from the FDA; however, its main purpose is to detail the data that provide documentation that it is reasonable to proceed with certain human trials with the drug.
Definitions

- **Investigational New Drug** is a new drug or biologic used in a *clinical investigation*

- **IND application** is a request for authorization to administer an investigational drug or biologic to humans or a marketed drug in a new indication and/or patient population
Definitions (continued)

- **Sponsor** is an individual, company, academic institution, or other organization that takes responsibility for and initiates a clinical investigation. The sponsor **is not** the “funding organization” by FDA definitions.

- **Investigator** is an individual under whose immediate direction a drug is administered or dispensed.

- **Sponsor-Investigator** is an individual who both initiates and conducts an investigation. The requirements/responsibilities under this part include both those applicable to an investigator and a sponsor.
APPLICABLE REGULATIONS

Drugs/Biologics

- The Federal Food, Drug, and Cosmetic Act (FD&C Act) gives the FDA authority to regulate drugs and biologics

- Code of Federal Regulations (CFR)
  - 21 CFR Part 312: Investigational New Drugs
21 CFR Part 312

• Contains procedures and requirements governing the use of investigational new drugs

• Applies to all clinical investigations of products that are subject to section 505 of the FD&C Act
<table>
<thead>
<tr>
<th>Regulations (continued)</th>
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<tbody>
<tr>
<td><strong>21 CFR § 11</strong></td>
<td>Electronic Records; Electronic Signatures</td>
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<tr>
<td><strong>21 CFR § 50</strong></td>
<td><em>FDA (21 CFR)</em> Protection of Human Subjects</td>
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<tr>
<td><strong>21 CFR § 54</strong></td>
<td>Financial Disclosure by Clinical Investigators</td>
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<tr>
<td><strong>21 CFR § 56</strong></td>
<td>Institutional Review Boards</td>
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<td><strong>21 CFR § 58</strong></td>
<td>Good Laboratory Practices</td>
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<td><strong>21 CFR § 211, § 810</strong></td>
<td>Good Manufacturing Practices</td>
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<td><strong>21 CFR § 1271</strong></td>
<td>Good Tissue Practices</td>
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</table>
Responsibilities of IND Sponsor-Investigators

Regulations (continued)

**Investigational Application**

- 21 CFR § 312 IND *Drugs and Biologics*
- 21 CFR § 812 IDE *Devices*
- 21 CFR § 809 IVD *In Vitro Diagnostics*

**Marketing Application**

- 21 CFR § 601 BLA *Biologics*
- 21 CFR § 314 NDA *Drugs*
- 21 CFR § 814 PMA *Devices*
Regulations (continued)

If a *Federally Funded* Study…

**45 CFR Part 46 (DHHS) Protection of Human Subjects**
Good Clinical Practice (GCP)

www.fda.gov/oc/gcp/

GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials.

Not Law, but FDA has adopted GCP.
(follow them…)
FDA RESPONSIBILITIES OF IND INVESTIGATORS

☑ Conduct study in compliance with GCP, protocol, & applicable IND/IDE regulations
☑ Ensuring informed consent of each subject is obtained (and retained)
☑ Personally conducting or supervising the investigation
☑ Protecting the rights, safety, and welfare of participants
☑ Ensure adequate medical care for the study participants
☑ Obtain necessary approvals from IRB
☑ Maintain and retain drug/device disposition and patient case history records
☑ Provide written reports to the IRB, as required
☑ Ensure changes are not implemented without prospective IRB/FDA approval
☑ Promptly report serious adverse events to the sponsor, IRB, and FDA
☑ Furnish Progress reports and Safety reports
☑ Ensure all study team members are informed about their obligations noted above
FDA RESPONSIBILITIES OF IND **SPONSOR-INVESTIGATORS**

In addition to the investigator responsibilities, sponsor-investigators are required to:

- Select qualified investigators at other institutions for multi-site trials
- Submit necessary amendments/supplements to FDA
- Provide information to other investigators and study staff to ensure that the study is performed properly
- Ensure that FDA and all participating investigators are promptly informed of significant new adverse effects or risks
- Ensure proper monitoring of the study
- Maintain adequate records
- Ensure the study is performed in accordance with the general investigational plan and protocol
- Maintain proper control of the study drug/device
When an IND IS Needed…

- When the study is using Drugs/Biologics that are not currently marketed
  - The Study is using a product that has not yet received approval in the United States by the FDA

- When the study is using currently marketed drugs:
  - The Study is intended for FDA submission as a well-controlled study in support of a new indication or labeling change
  - Intended to change the advertising of a prescription drug
  - Level of risk or acceptability of risk changed on account of route of administration, Dose level, Patient population
IND Application Contents

1. Form 1571 (Application)
2. Table of Contents of IND Application
3. Introductory Statement and General Investigational Plan
4. [Reserved]
5. Investigators’ Brochure
IND Application Contents (continued)

6. Protocol
7. Chemistry, Manufacturing, and Control Data
8. Pharmacology and Toxicology Information
9. Previous Human Experience
10. Additional Information
IND Contents – Further Details

1. Form FDA 1571
   – Handout
**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**PUBLIC HEALTH SERVICE**  
**FOOD AND DRUG ADMINISTRATION**  
**INVESTIGATIONAL NEW DRUG APPLICATION (IND)**  
**(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)**

<table>
<thead>
<tr>
<th>1. NAME OF SPONSOR</th>
<th>2. DATE OF SUBMISSION</th>
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<tr>
<th>3. ADDRESS (Number, Street, City, State and Zip Code)</th>
<th>4. TELEPHONE NUMBER (Include Area Code)</th>
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<tr>
<th>5. NAME(S) OF DRUG(s) (Include all applicable names. Trade, Generic, Chemical Code)</th>
<th>6. IND NUMBER (automatically assigned)</th>
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<tbody>
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<tr>
<th>7. INDICATION(S) (Covered by this submission)</th>
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<tr>
<th>8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:</th>
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<tbody>
<tr>
<td>PHASE 1</td>
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<tr>
<th>9. LIST NUMBER OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (IND) (21 CFR PART 312), NEW DRUG USE APPLICATIONS (21 CFR PART 314), AND PRODUCT LICENSE APPLICATIONS (21 CFR PART 315) REFERENCED TO THIS APPLICATION</th>
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<tr>
<th>10. IND submission should be consecutively numbered. The initial IND should be numbered “Serial number: 001.” The next submission (e.g., amendment, report, or correspondence) should be numbered “Serial Number: 001.” Subsequent submissions should be numbered consecutively in the order in which they are submitted.</th>
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<tbody>
<tr>
<td>SERIAL NUMBER</td>
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<tr>
<th>11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check one or more)</th>
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<tr>
<td>.initial investigational new drug application (IND)</td>
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<thead>
<tr>
<th>RESPONSE TO CLINICAL HOLD</th>
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<tbody>
<tr>
<td>PROTOCOL AMENDMENT(S):</td>
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<tr>
<td>INFORMATION AMENDMENT(S):</td>
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<tr>
<td>IND SAFETY REPORT(S):</td>
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<tr>
<td>NEW PROTOCOL</td>
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<tr>
<td>CHANGE IN PROTOCOL</td>
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<tr>
<td>NEW INVESTIGATOR</td>
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<thead>
<tr>
<th>RESPONSE TO FDA REQUEST FOR INFORMATION (Specify)</th>
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<tbody>
<tr>
<td>ANNUAL REPORT</td>
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<tr>
<td>GENERAL CORRESPONDENCE</td>
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<tr>
<td>OTHER</td>
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<th>CHECK ONLY IF APPLICABLE</th>
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** FOR FDA USE ONLY **

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<thead>
<tr>
<th>COMBINED RECEIPT STAMP</th>
<th>OBF RECEIPT STAMP</th>
<th>DIVISION ASSIGNMENT</th>
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**NOTE:** No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).
FDA Form 1571 (CFR 21 § 312.23(a)(1)(i-ix))

- Contractual agreement between sponsor and FDA
- Contains name of person responsible for conduct and progress of the study (Item 14)
- Contains name of person responsible for the review and evaluation of information relevant to the safety of the drug (Item 15)
- Sponsor or sponsor’s authorized representative agrees to conduct investigation in accordance with all applicable regulatory requirements (Item 16)
IND Contents – Further Details

6. Form FDA 1572 (Statement of Investigator)
   – Handout
Where do I submit the IND application?
(Submit in Triplicate)

**Drug:**
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Central Document Room
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

**Therapeutic Biological Product:**
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Therapeutic Biological Products Document Room
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

**Biologic Regulated by CBER:**
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Central Document Room
5901-B Ammendale Rd.
Rockville, MD 20852-1448
Responsibilities of IND Sponsor-Investigators

FDA RECEIPT OF THE IND:

- Upon receipt, IND number will be assigned and the application will be forwarded to the appropriate reviewing division.

- Reviewing division sends a letter with the IND number assigned, date of receipt of the original application, address where future submissions to the IND should be sent, and the name and telephone number of the FDA person to whom questions about the application should be directed.

- Studies shall not be initiated until 30 days after the date of receipt of the IND by FDA unless you receive earlier notification by FDA that studies may begin.
Labeling of Investigational Agents

21 CFR § 312.6

- Immediate packaging of product
  - “Caution: New Drug – Limited by Federal (or United States) law to investigational use”

- The labels and labeling shall not
  - Bear false and misleading statements
  - Represent that the drug is safe and effective for purposes being investigated
IND Maintenance (IND Amendments)

IND Amendment (Documents submitted to an active IND)

The 4 major types are...

- Protocol Amendments (21 CFR § 312.30)
- Information Amendments (21 CFR § 312.31)
- IND Safety Reports (21 CFR § 312.32)
- IND Annual Reports (21 CFR § 312.33)
# Safety Reporting Via MedWatch

## How to report

<table>
<thead>
<tr>
<th><strong>Patient/Subject</strong></th>
<th><strong>Product info</strong> (drug, biologic, device, etc.)</th>
<th><strong>Description of Event or Problem</strong></th>
<th><strong>Relevant tests/labs</strong></th>
<th><strong>Reporter</strong></th>
</tr>
</thead>
</table>

![MedWatch form image](image1.png)
## FDA Submissions - Responsibilities To FDA

<table>
<thead>
<tr>
<th>Submission</th>
<th>Timing</th>
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<tbody>
<tr>
<td><em>Amendment - New protocol</em></td>
<td>After IRB approval</td>
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<tr>
<td><em>Amendment - Changed protocol</em></td>
<td>At time of change</td>
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<tr>
<td><em>Amendment - New investigator</em></td>
<td>Within 30 days of being added</td>
</tr>
<tr>
<td><em>Amendment - Information</em></td>
<td>At time of occurrence</td>
</tr>
<tr>
<td><strong>IND safety report</strong> (unexpected AE that is serious and associated with the use of the drug or lab tests that suggest significant risk)**</td>
<td><strong>Within 15 calendar days of receiving notification</strong></td>
</tr>
<tr>
<td><strong>IND safety report</strong> (unexpected fatal or life threatening experience associated with the use of the drug)**</td>
<td><strong>Within 7 calendar days of receiving notification</strong></td>
</tr>
<tr>
<td><strong>Annual report</strong></td>
<td><strong>Within 60 days of anniversary of IND</strong></td>
</tr>
<tr>
<td><strong>Withdrawal of IND</strong></td>
<td>At time of withdrawal</td>
</tr>
<tr>
<td><strong>Discontinuation of investigation</strong></td>
<td>Within 5 working days of discontinuance</td>
</tr>
<tr>
<td><strong>Financial disclosure report</strong></td>
<td>At time of change</td>
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Monitoring the Trial

• Clinical Trial Monitor examines quality of trial conduct:
  – Perform on-site (if indicated, also off-site) evaluations of trial-related activities
  – Identify deviations in protocol conduct
  – Review documents for Adverse Events
  – Drug accountability – see also handout of IDS monitoring

• Extent and frequency of monitoring as appropriate:
  – Length, complexity, subject enrollment and other aspects of the trial
Monitoring the Trial: DSMB

- Additional measure of human subject protection
- Evaluates accumulating data from a clinical trial
- Generally, established by the sponsor
  - Select members, should be independent
  - Charter generally written by sponsor, may have consultation by members
- Recommendations regarding the conduct and design of the trial (safety and efficacy)
- *Does not* visit sites or substitute for clinical trial monitors
- Send DSMB reports to the IRB for review
Most **Common** Violations Noted by the FDA

- Failure to follow the protocol
  
  *example: Required testing is incomplete*

- Recordkeeping errors

- Informed consent problems/issues
Most Significant Violations noted by the FDA

- Enrollment of ineligible subjects
- Violation of protocol affecting safety
- Extensive data corrections and questionable changes
- Inadequate oversight of study personnel
  - Inappropriate delegation of authority
  - Poor oversight of sites
- No Informed consent
- Failure to communicate with IRB
Responsibilities of IND Sponsor-Investigators

Frequency of Issues in Past Warning Letters

- Consent: 53
- IRB: 41
- Protocol: 50
- Records: 56
- AEs: 14
- Device Accountability: 14
- Investigator Compliance: 10
- Monitoring: 25
MICHR IND/IDE Investigator Assistance Program

MIAP
MIAP Established to Provide Comprehensive:

- Regulatory Expertise…
- Regulatory Support…
- Regulatory Education Services…

To Faculty Investigators and their Team Involved In FDA Regulated Clinical Research At The University of Michigan
Responsibilities of IND Sponsor-Investigators

MIAP SERVICES OVERVIEW

• Agent/Device development strategy consultation
• IND/IDE consultation including determination of need for IND or IDE
• Pre-IND FDA meeting requests and support
• Protocol development
• IND/IDE application preparation and submission
• Clinical hold response preparation/submission
• Communication with the FDA, IRB and other regulatory bodies
• IND/IDE “maintenance” support
  – Safety report submissions
  – Protocol amendments to the FDA
  – Annual reports to the FDA
• Clinical Trial Monitoring
  – Investigators meetings
  – Site initiation visits
  – Interim site monitoring visits
  – Study close out activities
REGULATORY SERVICES MENU

IND & IDE EDUCATION SERVICES

☐ Investigator Responsibilities per FDA Regulations
☐ IND (21 CFR Part 312) Regulation Overview Training
☐ IDE (21 CFR Part 812) Regulation Overview Training
☐ Good Clinical Practice (GCP) Training & Coaching
☐ FDA Quality System Regulations & Good Manufacturing Practice Training
☐ Adverse Event Reporting Requirements for Investigator-Initiated Research
☐ IND Application Process Overview
☐ IDE Application Process Overview
☐ IND & IDE Annual FDA Reporting Requirements Training

INVESTIGATOR-SPONSOR REGULATORY ASSISTANCE

PRE-STUDY IND & IDE SUBMISSIONS PREP ASSISTANCE

☐ IND & IDE Requirement or Exemption Determinations
☐ IND & IDE Exemption Rationale Development
☐ Literature Search Assistance
☐ Protocol Development Assistance
☐ Data Safety Monitoring Plan (DSMP) Preparation Assistance
☐ SAE Form Development Assistance
☐ IND & IDE Submission Preparation & FDA Application Assistance
☐ FDA Contact & Correspondence Assistance

ON-GOING IND & IDE STUDY ASSISTANCE

☐ Clinical Trial Monitoring
☐ Safety & FDA SAE Vigilance Reporting
☐ IND & IDE FDA Annual Report Preparation and Submission
☐ DSMB Communications Assistance
☐ IND & IDE Protocol Amendment Preparation Assistance
☐ IND Amendments & Life Cycle Maintenance Assistance
☐ IDE Supplements & Life Cycle Maintenance Assistance
MIAP is here to help with INDs and IDEs

MIAP contacts:

Kevin Weatherwax, BS, CCRC, CCRA
Manager, Project Management and Monitoring Core;
MICHU IND/IDE Assistance Program (MIAP)
Michigan Institute for Clinical and Health Research (MICHU)
University of Michigan Health System
2800 Plymouth Road
NCRC, Building 400
Ann Arbor, MI 48109-2800
Campus Mail: 2800 Plymouth Road, Bldg. 400
Phone: 734-998-6275 Pager: 734-936-6266, #9912
Fax: 734-998-7318
Website: www.MICHU.umich.edu
kweath@med.umich.edu
Office of Human Research Compliance Review (OHRCR)

**Director**
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Office of the General Council

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Phone: 734-763-6240
kmorgens@umich.edu

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Jan Hewett, BSN, JD, IRBMED Director
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Fax: 734-763-1234
Pager: 3389
jhewett@umich.edu
Investigational Drug Service (IDS)

Helen Tamer, Pharm.D.
Clinical Pharmacist
Phone: 734-936-7469
Fax: 734-647-9302
Pager: 2960
hrtamer@umich.edu

Drug shipment address:
University of Michigan Hospital
Department of Pharmacy Services-IDS
UH B2D400
1500 E. Medical Center Drive
Ann Arbor, MI 48109-0008
Attention: Investigational Drug Service
Good Tissue, Manufacturing and Laboratory Practices (GTMLP)

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mstoe@med.umich.edu
FDA Website for INDs

http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm
Closing Thoughts and Q & A

Thanks for your attention!
Responsibilities of IND Sponsor-Investigators

Improving health one idea at a time —
by supporting every phase of research

Bringing researchers together —
by accelerating the pace of discovery

Connecting with the community —
by creating dialogue and collaboration