ORIENTATION FOR NEW CLINICAL RESEARCH PERSONNEL

WEEK 6

Presented by

NC TraCS Institute
UNC Office of Clinical Trials
UNC Network for Research Professionals
Overall Agenda for Orientation

Week 1 –
• Introduction to the series, NCRP and educational programs, Running a clinical trial beginning to end

Week 2 –
• UNC Institutional Review Board Processes, Conflict of Interest

Week 3 –
• Good Clinical Practice and Study Documentation, Informed Consent Processes, Research Monitor Access

Week 4 –
• Contracts and Clinical Trial Agreements, Billing Coverage Analysis, Budgeting and Accounting of Research Funds, Preparing and Executing NIH Budgets

Week 5 –
• Study Startup and Roles of Research Personnel, Recruitment Services and CDW, UNC Investigational Drug Services, Investigational Device Management Policy

Week 6 –
• Sponsor-Investigator Responsibilities, ClinicalTrials.gov and ICMJE requirements, Investigational Drug and Device studies at UNC
Sponsor-Investigator Responsibilities

Valorie Buchholz
Associate Director
Clinical Trial Quality Assurance Program
RESPONSIBILITIES OF A PI - Office of Human Research Protection (OHRP)

• obtaining and documenting informed consent of subjects or subjects’ legally authorized representatives prior to the subjects’ participation in the research, unless these requirements have been waived by the IRB (45 CFR 46.116; 45 CFR 46.117);

• obtaining prior approval from the IRB for any modifications of the previously approved research, including modifications to the informed consent process and document, except those necessary to eliminate apparent immediate hazards to subjects (45 CFR 46.103(b)(4)); and

• ensuring that progress reports and requests for continuing review and approval are submitted to the IRB in accordance with the policies, procedures, and actions of the IRB as referenced in the institution’s OHRP-approved Federalwide assurance (45 CFR 46.103(b)(4), 45 CFR 46.109(e), 45 CFR 46.115(a)(1)). In certain circumstances, investigators also would be responsible for meeting the following additional regulatory requirements:

• providing to the IRB prompt reports of any unanticipated problems involving risks to subjects or others 45 CFR 46.103(b)(5);

• providing to the IRB prompt reports of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB (45 CFR 46.103(b)(5)); and

• keeping certain records as required by the HHS regulations for at least three years after completion of the study (45 CFR 46.115(b)).
RESPONSIBILITIES OF A PI - FDA

• Ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan, and applicable regulations

• Protecting the rights, safety, and welfare of subjects under the investigator’s care

• Controlling drugs, biological products, and devices under investigation (21 CFR 312.60, 21 CFR 812.100)
PI RESPONSIBILITIES – Good Clinical Practice (GCP)

- Compliance with Protocol
- Study Personnel – Adequate Resource
- Medical Care of Trial Participants
- IRB Involvement
- Investigational Product(s)/Intervention
- Informed Consent of Participants

- Participant Recruitment
- Participant Informed Consent
- Records/Recording Data
- Essential Documents
- Progress Reports
- Safety Reporting

UNC has adopted GCP as the standard by which research with human subjects is conducted.

GCP is applicable to both biomedical and social/behavioral research.
INVESTIGATOR RESPONSIBILITIES

HUMAN SUBJECTS PROTECTION
TRAINING RESEARCH STAFF
IRB SUBMISSIONS/CONTINUING REVIEW
OBTAINING & MAINTAINING INFORMED CONSENT
STUDY CONDUCT/OVERSIGHT
SUPERVISION OF STAFF TO WHOM TRIAL RELATED DUTIES ARE DELEGATED
INVESTIGATIONAL PRODUCT ACCOUNTABILITY
ASSESSMENT OF ADVERSE EVENTS
RECORD RETENTION
BUT WHAT ABOUT WHEN THE PRINCIPAL INVESTIGATOR IS ALSO THE SPONSOR?
Who is a Sponsor- Investigator?

GCP

- An individual who both *initiates* and *conducts*, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

FDA

- An individual who both *initiates* and *conducts* an investigation, and under whose immediate direction the investigational product (IP) is administered or dispensed.
  - The term does not include any person other than an individual.
  - The requirements applicable to a sponsor-investigator include both those applicable to an investigator and a sponsor.

[21 CFR 312.3 and 21 CFR 812.3]
RESPONSIBILITIES (Single Site)

- MANAGE QUALITY THROUGHOUT THE TRIAL
- SELECTING QUALIFIED MONITORS TO MONITOR THE INVESTIGATION
- ENSURING THE TRIAL IS CONDUCTED ACCORDING TO THE PROTOCOL
- REGISTERING TRIAL ON CLINICALTRIALS.GOV AND REPORTING RESULTS IF APPLICABLE
Key Responsibilities

• Monitoring of the clinical investigation
  • Risk based plan
    • Identify Critical Data Points and Processes
      • Informed Consent Obtained Properly
      • Eligibility and Protocol Compliance
      • Data Verification Related to Study End Points
      • IP Accountability (If Applicable)

• ClinicalTrials.gov
  • Timing for registration based on multiple factors – see OCT website for additional information

Multi-Site Trials
RESPONSIBILITIES MULTI-SITE TRIALS

- Maintaining a trail master file inclusive of essential documents
- Selecting qualified investigators
- Providing information to investigators to conduct the trial properly
- Monitoring the investigators
- Maintaining records showing receipt, shipment, disposition of the investigational product
- Informing investigators of significant new adverse events or risks
Key Responsibilities

Collecting Essential Documents From Sites:
• CVs/Licenses
• IRB Approvals (inclusive of approved Informed Consent Documents)
• Signatures Pages inclusive of each amendment or version
  • (Protocol and Investigator Brochure/Device Manual if applicable)
• Lab Accreditations & Normal Ranges (if applicable)
• Trial Initiation Report
• Relevant Communications with Sites
Key Responsibilities (Continued)

• Notification To Investigators of Any New Risks Identified or Safety Information
• Signed, Completed Case Report Forms
• Delegation/Signature Logs
• Shipping Records of Investigational Product
• Ensuring any additional sites are added to the ClinicalTrials.gov record
If Conducted Under an IND or IDE You’ll Also Need to Collect from Sites

• 1572s or Investigator Agreement
• Financial Disclosure Forms
As Well As.......  

• Submission and maintenance of Regulatory Authority submissions (hint – FDA 😊)  
  • New protocols under the same IND/IDE  
  • Annual progress reports  
  • Significant protocol revisions  
  • Change in PI  
  • Adding additional sites  
  • Safety reporting  
    • Notify FDA of any unexpected fatal or life-threatening suspected adverse reactions within 7 calendar days  
    • Notify FDA (and participating investigators) via an IND safety report of potential serious risks within 15 calendar days  

Resources offered through NC TraCS and ReGARDD.org
Risk factors for non-compliance

• Lack of knowledge
• Poor supervision and training of study staff
• Insufficient investigator involvement in study conduct
• Inappropriate delegation of study tasks to unqualified persons
• Overworked investigator and study staff (e.g., too many subjects, complex study with large data collection, too many concurrent studies)
Frequent Findings during CTQA Reviews

- Missing consent documents including HIPAA auths
- Missing essential documents
- Lack of training documentation
- Lack of correspondence
- Lack of database management and review
What non-compliance can lead to.....
Retraction Watch Database
(http://retractiondatabase.org/RetractionSearch.aspx?)

42 Publications Associated with UNC Researchers Retracted since 2003

- Results Not Reproducible
- Unreliable Results
- Falsification/Fabrication of Data
- Concerns Issues About Data
- Investigation by Company/Institution
Resources

• ICH GCP E6(R2) dated 9November 2016:  

• Office of Clinical Trials - Links to internal and external resources (FDA, OHRP, NIH, Associations, Policies, etc.): http://research.unc.edu/clinical-trials/resources/

• Office of Clinical Trials - Links to Forms/Templates (DOA log, SAE log, Start-up Checklist, Training log, etc.): http://research.unc.edu/clinical-trials/resources/forms/

• NC TraCS – Protocol development, data management, IND/IDE submissions – maintenance: https://tracs.unc.edu/
THANK YOU!!
Trial Registration & results Reporting at ClinicalTrials.gov: FDA, ICMJE, NIH, and CMS

Monica Coudurier
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What is ClinicalTrials.gov?

• Web-based registry maintained by National Library of Medicine (NLM) providing regularly updated information for federally and privately supported clinical trials
• Mandated by 1997 FDA Modernization Act (FDAMA)
• First version publicly available February 29, 2000
• Expanded by FDA Amendments Act 2007 (FDAAA)
  – Requires certification Form FDA 3674
• Final Rule:
  
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Types of Information Seen in CT.gov

- Some information provided in ClinicalTrials.gov records includes the following:
  - Disease or condition and experimental treatments studied
  - Title, description, and design of study
  - Requirements for participation
  - Location(s) where the study is available
  - Overall study status
  - Recruitment contact information
  - Links to relevant information at other health Web sites, such as MedlinePlus and PubMed
What Trials Must be Registered?

There are 4 independent bodies requiring trial registry:

- **ICMJE** International Committee of Medical Journal Editors
- **FDA** FDAAA Section 801/Code of Federal Regulations
- **NIH** National Institutes of Health
- **CMS** Centers for Medicare & Medicaid Services
The International Committee of Medical Journal Editors (ICMJE) Policy

Per the ICMJE, any trial meeting their definition of “clinical trial” must be registered prior to enrollment of the 1st subject to be considered for publication: “any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome.”

• Health-related intervention includes any intervention used to modify a biomedical or health-related outcome (e.g., drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes).

• Health outcome includes any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events.
Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator or the study protocol) will not require registration.
Individual Participant Data (IPD) Sharing

• Manuscripts submitted as of July 2018 must contain a data sharing statement

• Clinical trials initiated on/after Jan 2019 must include a data sharing plan in the trial registration record
  – Specific emphasis placed on presence of plan at registration

• Per U.S. Office for Human Research Protections, separate participant consent not required for sharing deidentified provided the appropriate conditions are met

• UNC has suggested language to adapt to this field located within the ClinicalTrials.gov section of the OCT website: (https://research.unc.edu/clinical-trials/clinical-trials-gov/data-sharing-guidance/).
Pertains to trials using an FDA-regulated intervention--irrespective of approval status--and meeting the regulatory definition of an Applicable Clinical Trial (ACT).

• **ACTs** generally include:
  
  – Trials of **Drugs** and **Biologics**: Controlled, clinical investigations, (other than Phase 1 investigations), of a product subject to FDA regulation *(If efficacy is an endpoint of Phase I study, it must be registered).*
  
  – Trials of **Devices**: Controlled trial with health outcomes, other than small feasibility studies, and pediatric post market surveillance.
NIH requires Registration and Results reporting of all trials funded either in whole or in part that meet their definition of a clinical trial.

- Includes Phase 1 studies
- Independent of FDAAA requirements
- Applies to Extramural and Intramural award programs
- Funding applications submitted on or after 01/18/2017 requesting support for trials initiated after 01/18/2017 (not applicable to ongoing clinical trials in non-competing awards)

Clinical trials using NIH-supported infrastructure, not receiving NIH funds for conduct subject to policy
NIH Policy: Clinical Trial Definition

“Clinical trial” means “a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.”

• NIH “clinical trial” definition is broader than the term Applicable Clinical Trial (ACT) defined by FDAAA
The study is a clinical trial
Centers for Medicare and Medicaid Services (CMS)

• January 1, 2014 - CMS began requiring the NCT (National Clinical Trial) number on all clinical trial-associated claims submitted to Medicare.

  » available only from ClinicalTrials.gov
  » must be entered into CRMS
  » claims submitted without NCT rejected
Trial Registration Deadlines

• **ICMJE** — Study must be registered *prior* to enrollment of first subject.
  
  *Publication eligibility*

• **FDAAA** — ACTs must be registered no later than 21 days after enrollment of the first subject.
  
  *Required by US Public Law and must be done to avoid $$ penalties*

• **NIH** — not later than 21 calendar days after the enrollment of the first participant
  
  *Required by US Public Law and must be done to avoid $$ penalties*

• **CMS** — Prior to claims submission
  
  *To avoid claim rejection*
## Trial Registration Overview

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<th>Phase 1</th>
<th>Phases 2-4</th>
<th>Device</th>
<th>Other Interventional*</th>
<th>Observational</th>
<th>Post Results?</th>
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<td>Within 21 days of 1st subject’s enrollment</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>FDA</td>
<td>Within 21 days of 1st subject’s enrollment</td>
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<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>CMS</td>
<td>Prior to claims submission (for Qualifying Clinical Trials)</td>
<td>Yes (if qualifying)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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* Health-related or Behavioral Interventional Trials
Who is Responsible for Registering Trials? Reporting results?

Clinicaltrials.gov registration is the responsibility of the trial **Sponsor**:

- UNC Investigator initiates and sponsors trial – **PI registers**
  - Trial in which PI obtains industry funds
  - NIH or other grant funded trial (external or internal grants)
  - UNC PI holds an IND or IDE

- Industry sponsored + initiated trial – **Industry sponsor registers**
Getting Started
CT.gov User Account Set-Up

– If UNC PI responsible for registry, CT.gov user account set-up and record assistance available through:
– Each person requiring record access must have their own user account

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<tr>
<td>Monica Coudurier</td>
<td>Marie Malikowski</td>
</tr>
<tr>
<td><a href="mailto:m_coudurier@unc.edu">m_coudurier@unc.edu</a></td>
<td><a href="mailto:marie_malikowski@med.unc.edu">marie_malikowski@med.unc.edu</a></td>
</tr>
<tr>
<td>(919) 843-2333</td>
<td>(919) 966-4432</td>
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http://research.unc.edu/clinical-trials/clinical-trials-gov/
Which Studies Require Results Entry?

- **FDAAA 801:** trials meeting the definition of “Applicable Clinical Trial” or ACT (regardless of whether the study has an IND or IDE)

- **NIH** (Final Rule effective January 18, 2017)
  All Federally funded studies meeting “clinical trial” definition

ICMJE and CMS do **not** require results reporting
ClinicalTrials.gov results reporting should be final within 1 year of ‘Actual’ Primary Completion date.

- **Primary Completion Date**: date that the last participant was examined or received intervention for final collection of primary outcome-related data.

- ClinicalTrials.gov minimally takes 30 days to review records with results.
- Multiple reviews are typical.

**START EARLY!!**
Complementary Initiatives

• Must submit full protocol and statistical analysis plan along with results submission.

• ACT definition expanded to include unapproved products

• All single & multi-arm/group studies with prespecified outcome measures considered “controlled.”

• NIH will post records within specified time despite QC review status (disclaimer citing concern may be posted)

• Reporting frequencies changed
Record Upkeep: Following Registration

• Ensure the information is complete, accurate, and updated annually (minimum), or as changes occur.

• Record Verification date field must be updated each time

• More frequent updates required for certain data elements:
  – 30 day Reporting Frequency:
    • Overall Recruitment Status
    • Primary Completion Date
    • Study Completion Date
    • Protocol amendments resulting in subject updates following IRB approval
Quality Control Corrections

- Within ‘X’ days of electronic notification (i.e., email), all apparent errors, deficiencies, and/or inconsistencies identified during quality control review must be addressed and record re-released to ClinicalTrials.gov.

<table>
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<th>Record Type</th>
<th>Completed not later than:</th>
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<tr>
<td>Protocol registration records</td>
<td>15 calendar days</td>
</tr>
<tr>
<td>Results information</td>
<td>25 calendar days</td>
</tr>
</tbody>
</table>
New Rule--Useful Links

• Federal Register Notice: HHS Final Rule

• Federal Register Notice: NIH Policy

• Summary of Changes: HHS Final Rule and NIH Policy
Monetary Penalties

What are the penalties for failing to comply with registration and/or results reporting requirements for an “Applicable Clinical Trial” or NIH-funded study?

• Penalties for responsible parties failing to register or providing false or misleading information in connection with applicable clinical trials may include civil monetary penalties (up to $11,569/day)

• Federally-funded trials, the withholding or recovery of grant funds.
• Award grantees are permitted to charge the salaries of administrative and clerical staff as a direct cost [Ref. below]. Such staff could assist investigators in meeting their responsibilities under the policy.

• In addition, administrative costs can be covered through indirect cost recovery.

  - 45 CFR 75.413(c) and Chapter 8.1.1.6, Direct Charging Salaries of Administrative and Clerical Staff. NIH Grants Policy Statement.
Questions
Investigational New Drug (IND) and Investigational Device Exemption (IDE) Submissions and Best Practices

Amanda Wood, B.S., RAC, CCRP
IND/IDE Program Coordinator
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Protocol Planning and Startup Tasks

**SRC thoroughly reviews for:**
- Scientific Merit and Importance
- Statistical Integrity
- Feasibility
- Clear Aims
- Relevant Outcome Measures
- Appropriate Data Management and Safety Monitoring
- GCP, FDA, and UNC Requirements

**IRB thoroughly reviews for**
- Subject Rights and Welfare
- Ethical Conduct
- Personnel Training and Background
- Transparency of Risks and Benefits
- Equal Opportunity and Parity
- Adherence to Federal/State laws, OHRP, UNC policies

**Confidential and Secure Data**
- CRF Creation, Database Design
- Evaluate safety plan
- Plan for AE / SAE Reporting
- SRC Review, then IRB Review

**Plan for CT.gov registration and data entry. Talk to Monica Coudurier early in the process.**

**Formulate Study Design**
- Clearly define objectives and outcome measures – Including statistical analysis plan

**Determine subject selection, statistically justify enrollment goal**

**Plan for interim data analysis for feasibility/efficacy.**

**Clinical Feasibility Analysis**
- Budget Analysis
- Data Collection and Storage
- Human Subject Protection / Safety Monitoring Plan

**Submit to SRC, then IRB for approval**

**FINER: Feasible, Interesting, Novel, Ethical, Relevant**

**Account for dropouts in analysis**

**Objectives should be associated with measurable endpoints**

**Assess clinical resources for study feasibility. Do you need special labs, procedures etc?**

**SRC Review, then IRB Review**

**SRC thoroughly reviews for:**
- Scientific Merit and Importance
- Statistical Integrity
- Feasibility
- Clear Aims
- Relevant Outcome Measures
- Appropriate Data Management and Safety Monitoring
- GCP, FDA, and UNC Requirements
Active Study Implementation

**Coordinators, Finance, Regulatory, Sub-Investigators etc.**
Train on applicable elements of protocol

**Assess changes, revise protocol, and train accordingly.**
Ensure version control

**IRB review and approval of modifications**

**Register Protocol with CT.gov**

**Streamline Study Execution**

**Interim data analysis for feasibility / efficacy. Safety analysis if needed.**

**Protocol Modifications**

**If mods require consent changes, must report to CT.gov**

**IDS, Clinic Staff, Radiology, Lab, Infusion, etc.**
Train on applicable elements of protocol

**Data Safety and Monitoring Plan, Or DSMB**

**Must update CT.gov within 30 days of IRB approval.**

**Must register PRIOR to enrollment, per ICMJE requirements.**
Protocol Planning and Startup Tasks

Active Study Implementation

Study Closure

Final data analysis, compilation of results

- Review final report and formally close
- Study Publication

Close Protocol with CT.gov, report results

Close Protocol with CT.gov, report results

Close Study with IRB

Study Publication

Study Publication
Outline

• Investigational New Drug (IND) Submission
  – Exempt Studies
  – IND submission and maintenance
• Investigational Device Exemption Submission
  – Exempt and Abbreviated IDE studies
  – IDE submission and maintenance
What is a Drug?

A drug is anything that meets the definition of a drug per the FD&C Act (201(g)(1)). . .

“. . .articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals. . .”

“...a substance (other than food) intended to affect the structure or any function of the body”

“...compounds administered to blunt or provoke a physiological response or to study the mechanism of action or metabolism of a drug.”
What is an **Investigational Drug**?

- An article that is not approved for marketing in the US as a drug
- Approved drug that is not used according to the approved label (or used in a new combination of approved drugs)

“For the purposes [of IND regulations], an experiment is any use of a drug [whether approved or unapproved] except for the use of a *marketed drug* in the course of medical practice.” - 21 CFR 312.2(b)
Dietary Supplements: Drugs?

• A dietary supplement is not considered a drug if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose).

• However, if the clinical investigation is intended to evaluate the dietary supplement’s ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required.
Investigational New Drug Application

An Investigational New Drug (IND) application is a request to the FDA to provide authorization to administer:

• an investigational drug (or biologic) to humans (always requires an IND application)

• OR a previously marketed drug in a new indication and/or patient population – i.e. Not according to approved labeling. (may be exempt from IND requirements)
Criteria for IND Exempt Studies

FIRST – The study must be the “investigation of a drug product that is lawfully marketed in the United States” 21 CFR 312.2(b)(1)

• If it is not marketed in the US, but approved in other countries, you will still need an IND
Criteria for IND Exempt Studies

There are 5 criteria that allow a study to be exempt from requiring an IND.

**All 5 criteria must be met!**

1. The study is not designed to support approval of a new indication or a change in label

2. The study is not intended to support a significant change in the advertising for the product
Criteria for IND Exempt Studies

3. If the study does not involve a route of administration, dosage level, or patient population that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug.

4. The study is conducted in compliance with the IRB and informed consent regulations.

5. The investigation is not intended to promote or commercialize the drug product.

21 CFR 312.2(b)
Who determines if the study is IND Exempt?

The Investigator:

- Because the assessment of risks involved in a therapeutic procedure is an everyday part of the practice of medicine, the individual investigator should usually be able to determine the applicability of the exemption.”
  
  - FDA guidance

The IRB:

- When filling out the application in IRBIS, download the IND-Exemption checklist here: [http://research.unc.edu/files/2013/04/CCM3_039765.docx](http://research.unc.edu/files/2013/04/CCM3_039765.docx) you will need to justify that you meet all 5 of the exemption requirements.

The FDA:

- Submit either a Request for IND Exemption, or a full IND Submission with a statement in the cover letter requesting a determination on IND exemption. There are advantages/disadvantages to both types of submissions.
Preparing and Submitting an IND

IND Submission Template can be found at www.ReGARDD.org
Reasons for IND submissions

- **Investigator-Initiated IND** – research driven, with publication as the main goal
- **Expanded Access IND** – For single patients, including emergency settings; intermediate or large sized populations with the intent to treat, not to obtain safety information.
- **Commercial IND** – submitted with the intent to bring to market or change current labeling
# IND Submission Format and Content

1. Form 1571 (cover sheet), Form 3674
2. Table of Contents
3. Introductory Statement
4. General Investigational Plan
5. Investigator’s Brochure
6. Proposed Clinical Research (Includes forms 1572, 3454, 3455)
7. Chemistry, Manufacturing and Control Data (CMC)
8. Pharmacology and Toxicology Data
9. Previous Human Experience
10. Additional Information
11. Relevant Informations
IND Submission Format and Content - FORMS

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9. Previous Human Experience
10. Additional Information
11. Relevant Informations
FDA form 1571 - 1) to obtain agreement from the sponsor (or sponsor-investigator) to conduct research according to all appropriate FDA regulations; and 2) to serve as a cover sheet for all submissions to the FDA on behalf of a particular IND.
FDA form 3674 - Signed statement from the sponsor/investigator that they will comply with clinicaltrials.gov requirements concerning their investigation.

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<td>FOR DEVICES: Include AnyN/NA: Common or Java Name(s), Classification, Trade or Proprietary Name(s) and/or Model Number(s) (Attach extra pages as necessary)</td>
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<tr>
<th>CERTIFICATION STATEMENT / INFORMATION</th>
</tr>
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<tbody>
<tr>
<td>9. CHECK ONLY ONE OF THE FOLLOWING BOXES (please instructions for additional information and explanation)</td>
</tr>
<tr>
<td>A. I certify that the requirements of 42 U.S.C. § 263(j), Section 421(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.</td>
</tr>
<tr>
<td>B. I certify that the requirements of 42 U.S.C. § 263(j), Section 421(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.</td>
</tr>
<tr>
<td>C. I certify that the requirements of 42 U.S.C. § 263(j), Section 421(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.</td>
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| X NCT Number(s) |

The undersigned declares, to the best of their knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 263(j)(1)(B), section 420(j)(1)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 307 of the Federal Food, Drug, and Cosmetic Act. Warning: A willfully false or knowing false statement is a criminal offense. U.S. Code, title 18, section 1001. |

| SIGNATURE OF SPONSOR/APPLICANT/SUBMITTER OR AN AUTHORIZED REPRESENTATIVE (Sign) |
| 11. NAME AND TITLE OF THE PERSON WHO SIGNED IN NO. 11 |
| (Name) | (Title) |

| ADDRESS (Number, Street, State, and ZIP Code) (of person identified in Nos. 11 and 12) |
| 14. TELEPHONE AND FAX NUMBERS (Include Area Code) |
| (Tel) | (Fax) |

<table>
<thead>
<tr>
<th>15. DATE OF CERTIFICATION</th>
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</table>
FDA form 1572 - Agreement from the Investigator that research will be compliant with FDA regulations. Contains clinical site and investigator info to assure the FDA that all investigators have the experience/background needed to conduct the trial.

<table>
<thead>
<tr>
<th>DEPARTMENT OF HEALTH AND HUMAN SERVICES</th>
<th>FDA form 1572 (2016)</th>
<th>PREVIOUS EDITION IS OBSOLETE.</th>
</tr>
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<tbody>
<tr>
<td>FOOD AND DRUG ADMINISTRATION</td>
<td>FORM FDA 1572 (2016)</td>
<td>Page 1 of 2</td>
</tr>
<tr>
<td>STATEMENT OF INVESTIGATOR</td>
<td></td>
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<tr>
<td><strong>(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)</strong></td>
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<td>(See instructions on reverse side.)</td>
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<tr>
<td><strong>Name of Investigator</strong></td>
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**EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION**

- **Curriculum Vitae**
- **Other Statement of Qualifications**

**Name of Medical School, Hospital, or Other Research Facility WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED**

**Name of Clinical Laboratory Facility**

**Name of Institutional Review Board (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY/IES**

**Names of Subinvestigators (if not applicable, enter "None")**

**PROVIDE THE FOLLOWING CLINICAL PROTOCOL INFORMATION**

- **For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.**
- **For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any, the clinical uses to be investigated, characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study, and copies or a description of case report forms to be used.**

**COMMITMENTS**

- I agree to conduct the study(s) in accordance with the relevant clinical protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- I agree to personally conduct or supervise the described investigator(s).
- I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.
- I agree to assure that all associates, colleagues, and employees assisting in the conduct of the study(s) are informed about their obligations in meeting the above commitments.
- I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- I agree to comply with all other requirements regarding the obligations of clinical investigators and all pertinent requirements in 21 CFR Part 312.

**INSTRUCTIONS FOR COMPLETING FORM FDA 1572**

1. Complete all sections. Provide a separate page if additional space is needed.
2. Provide curriculum vitae or other statement of qualifications as described in Section 2.
3. Provide protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND OTHER DOCUMENTS BEING PROVIDED TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

**DATE**

**SIGNATURE OF INVESTIGATOR**

**WARNING:** A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.

The information below applies only to requirements of the Paperwork Reduction Act of 1995. The burden time for this collection of information is estimated to average 100 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed, and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden on the address to the right.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number.
# Form 3454 and 3455 Certification and Disclosure of Financial Interests

## Certification: Financial Interests and Arrangements of Clinical Investigators

**TO BE COMPLETED BY APPLICANT**

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(b).

Please mark the applicable check box:

- [ ] (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).
- [ ] (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(b)). There was no propriety interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)), and was not the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).
- [ ] (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

### Name

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<tr>
<th>NAME</th>
<th>TITLE</th>
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### Firm/Organization

<table>
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<tr>
<th>FIRM/ORGANIZATION</th>
<th>SIGNATURE</th>
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This section applies only to the requirements of the Paperwork Reduction Act of 1980. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Federal Register notices for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

**DO NOT send your completed form to the PRA Staff email address below.**

**Department of Health and Human Services**  
**Food and Drug Administration**  
**Office of Information**  
**PRA000935@HHS.gov**

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# Disclosure: Financial Interests and Arrangements of Clinical Investigators

**TO BE COMPLETED BY APPLICANT**

The following information concerning , who participated as a clinical investigator in the submitted study is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check box:

- [ ] any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- [ ] any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainers for ongoing consultation, or honoraria;
- [ ] any proprietary interest in the product tested in the covered study held by the clinical investigator;
- [ ] any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual’s disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

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**DO NOT send your completed form to the PRA Staff email address below.**

**Department of Health and Human Services**  
**Food and Drug Administration**  
**Office of Information**  
**PRA000935@HHS.gov**
IND Submission Format and Content

1. Form 1571 (cover sheet), Form 3674
2. Table of Contents
3. Introductory Statement
4. General Investigational Plan
5. Investigator’s Brochure
6. Proposed Clinical Research (Includes forms 1572, 3454, 3455)
7. Chemistry, Manufacturing and Control Data (CMC)
8. Pharmacology and Toxicology Data
9. Previous Human Experience
10. Additional Information
11. Relevant Informations

Can refer to drug labeling or to letter of authorization (cross reference letter) for these sections
Approved Labeling vs. Letter of Authorization

**Approved Labeling**: Use when investigating an approved, marketed drug.

- Contains all pertinent info on safety, manufacturing, and previous human experience that the FDA needs to consider. [http://dailymed.nlm.nih.gov/dailymed/about.cfm](http://dailymed.nlm.nih.gov/dailymed/about.cfm)
- Include a copy of the labeling in your submission

**Letter of Authorization**: Use when investigating a new drug that has an existing IND elsewhere.

- This is a letter from a sponsor (company) providing their permission to the FDA to reference the named materials in support of your IND submission. Don’t re-invent the wheel!
- Include a copy of the letter in your submission
5 – Investigator’s Brochure

• Investigator’s brochures are not mandatory for investigator initiated trials, but are very useful for multi-center studies.

• If not including an IB, you may state the following “In accordance with 21 CFR Part 312.55(a), an Investigator’s Brochure is not required for a sponsor-investigator IND.”

OR

• Refer to the approved drug labeling (Often included as an appendix at the end of the submission)
6 – Proposed Clinical Research

• Includes the complete study protocol. We highly encourage using the NIH-FDA Protocol Template.

• Can include the informed consent document, although this is not required. The FDA may request to see the informed consent document if not included, however.

• FDA form 1572, Sponsor-Investigator CV, Medical License, and Financial Disclosure forms (FDA Forms 3454 and 3455). Sub-investigator documents do not need to be submitted, but must be kept current in the regulatory binder.
If the investigational drug has been marketed, this section may be covered by referring to the product labeling. Alternatively, it might be appropriate to refer to a ‘Letter of Authorization’ if using a drug provided by a commercial company.

If you are manufacturing your own compound, highly detailed information regarding the chemical characteristics and processing must be included here, highlighting adherence to Good Manufacturing Practices (GMP)
8 – Pharmacology and Toxicology

• Similar to section 7, if the investigational drug has been marketed, this section may be covered by referring to the product labeling. Alternatively, it might be appropriate to refer to a ‘Letter of Authorization’ if using a drug provided by a commercial company.

• If you are manufacturing your own compound, include information about pharmacological and toxicological (laboratory animals or in vitro) studies on the basis of which the sponsor of the IND application has concluded that it is reasonably safe to conduct the proposed clinical investigations.
9 – Previous Human Experience

• Similar to section 7 and 8, if the investigational drug has been marketed, this section may be covered by referring to the product labeling. Alternatively, it might be appropriate to refer to a ‘Letter of Authorization’ if using a drug provided by a commercial company.

• It is also beneficial to include summaries (if known) of prior clinical research experience for the drug.
Appendices

• Appendices may help to organize the submission, and include information that the FDA may use as a reference when reviewing the presented information.

• Package inserts, LOAs, reprints of publications, investigator CVs, etc
IND Submission Formatting and Instructions

• Submission should be in 12 point Times New Roman
• Include a brief cover letter signed by Sponsor
• Three copies (original and 2 exact copies) must be sent to the FDA at the address below:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

( use this address for drugs)

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

( use this address for biologics (i.e. vaccines, blood components, etc.)
IND Submission Formatting and Instructions

• A "courtesy e-copy" may be sent as well. The e-copy should be an exact copy of the original, in PDF format. If use of multimedia is necessary for the submission (i.e. large detailed images, or videos), then the submission cover letter should indicate the additional information contained on the e-copy. The e-copy is submitted on a CD, DVD, or thumb drive. Make sure that the information is not encrypted (especially common on thumb drives).

• The paper submissions should be bound individually in 3-hole punch ACCO-style folders. The original submission should be in a gray folder. The other two copies may be in different colors. Submissions that are inadequately bound will not be reviewed.
IND Submission Formatting and Instructions

• A label should be attached to the front of each folder. The e-copy should also have a label.

INITIAL IND APPLICATION
Serial No. 0000

<Sponsor Name>
<Date of Submission>
Original Copy (or Duplicate Copy 1 of 2)
What Next?

• Upon receipt of an IND application, FDA will notify the sponsor of the date it receives the application through an IND acknowledgment letter. The acknowledgment letter will also contain the IND number, the FDA review division assigned to review the IND, and the FDA point of contact.

• The study may proceed 30 days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold. In the absence of hearing from FDA, the sponsor is encouraged to contact FDA to ensure the study may proceed.
Clinical Hold ?!

If an IND has been placed on clinical hold, the study may not be initiated until the Agency has contacted you telling you that the study may proceed.

• **Complete Clinical Hold:** A delay or suspension of all clinical work requested under an IND.

• **Partial Clinical Hold:** A delay or suspension of only part of the clinical work requested under the IND (e.g., a specific protocol or part of a protocol is not allowed to proceed; however, other protocols or parts of the protocol are allowed to proceed under the IND).
Maintaining an IND

IND Templates can be found at www.ReGARDD.org
Annual Reporting

• IND application sponsors are expected to submit brief reports of the progress of the investigations conducted under their respective IND application within 60 days of the anniversary date that the application went into effect.

• Information in report should include: Summary Information, Protocol Updates, Update to General Investigational plan, etc. (refer to template for guidance)

• Submit in triplicate, and include signed Form 1571
Protocol Amendments

- **New Protocol Amendment**: INDs can include multiple protocols that study the same drug and indication. Include a brief summary and rationale of the new study, and a complete protocol.

- **Change in Protocol**: include a brief summary of the differences between revised protocol and previous protocol(s), rationale for the proposed change, a copy of the revised/updated protocol, and a track-changes version of the protocol.

- **New Investigator/New Site**: FDA must be notified within 30 days. Include new 1572 and CV/Med License

- **Information Amendment**: Anything that doesn’t fall under the above topics, or safety reporting. Usually for manufacturing or toxicology updates, or for study closure.
Safety Reporting

IND application sponsors are required to notify FDA (and all participating investigators) in a written safety report of any adverse experience (AE) associated with the use of the drug that is both serious and unexpected.
Safety Reporting

There are two kinds of Safety Report submissions:

- **Initial Written Report** - IND sponsor must report any adverse reaction or suspected adverse reaction to study treatment that is both serious and unexpected to FDA as soon as possible but no later than **7 calendar days** following the sponsor's initial receipt of the information.

- **Follow-Up to the Written Report** - Any relevant additional information obtained by the sponsor during investigation of the AE that pertains to a previously submitted IND safety report must be submitted as a Follow-up IND Safety Report. Such reports should be submitted without delay, as soon as the information is available but no later than **15 calendar days** after the sponsor receives the information.
Safety Report Submission Format

• Form FDA 3500A (Mandatory MedWatch)
  – For clinical trial safety reports, for use by IND reporters, manufacturers, distributors, importers, user facilities personnel
  – **Do not use:** Form FDA 3500 (Voluntary MedWatch), which is used by healthcare professionals, consumers, and patients
Investigational Device Exemptions (IDEs)
What is a Medical Device?

It's an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or other similar or related article or component part or accessory which:

• is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease

• is intended to affect the structure or any function of the body

• achieve its primary intended purposes through physical action and NOT chemical or metabolic action
**In Vitro Diagnostics and Software as Devices.**

- **IVDs** are those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.

- **Apps and software** intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease can be classified as devices. However, the FDA is selective in regulating software and apps. (21st Century Cures Act)
Investigational Device Exemption (IDE)?

- An IDE is a regulatory submission that permits clinical investigation of devices to determine safety and effectiveness.
- An FDA-approved Investigational Device Exemption Application (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device (21 CFR 812.1).
What Studies are IDE-Exempt?

• If the objective of the study is not to test the safety or effectiveness of the device, then the study would not fall within the scope of IDE Regulations. (Devices used as “tools”)

• A **diagnostic device** that is noninvasive, non-significant risk, does not introduce energy, and is confirmed by another established procedure.

• A device undergoing a consumer preference testing, or testing that is not for the purpose of determining safety or effectiveness.

• A legally marketed device when used in accordance with its labeling. (Comparative effectiveness)
In order to decide which type of IDE is needed, an SR/NSR determination is required. That determination can be made by the IRB or the FDA

- A non-significant risk (NSR) study requires an Abbreviated IDE and is solely overseen by an IRB.
- A significant risk (SR) study requires an IDE that is reviewed by the FDA.
Abbreviated IDE Regulations

• Investigator and IRB determine that the study is non-significant risk. Oversight is provided by the IRB. FDA does not have direct oversight.

• When filling out the application in IRBIS, download the Investigational Device Worksheet here: https://research.unc.edu/files/2016/04/Investigational-Device-Worksheet-ver.10-05-2016.pdf you will need to justify that you meet all of the exemption or abbreviated IDE requirements.
**Significant Risk Investigations = IDE submission.**

- **A significant risk** device is one that:
  - Is intended as an implant and presents a potential for serious risk to the health, safety, and welfare of a subject.
  - Is used to support or sustain human life.
  - Is of substantial importance in diagnosing, curing, mitigating, or treating disease and/or otherwise preventing impairment of human health.
  - Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

- The study risk determination is based on the proposed use of a device in an investigation, and not on the device alone.
Preparing and Submitting an IDE

IDE Submission Template can be found at www.ReGARDD.org
IDE Submission

1. Cover Sheet
2. Name and Address of the Sponsor
4. Investigational Plan
5. Manufacturing Information
6. Investigators Agreement
7. Investigators Certification
8. IRB Information
9. Name and Address of Investigators Institution
10. Financial Claims
11. Environmental Assessment
12. Labeling
13. Informed Consent
14. Additional Information
4 - Investigational Plan

Includes several sections:

• Description of the purpose of the device and the objectives of the study
• Study Protocol – Again, the NIH-FDA template is recommended.
• Risk Analysis
• Description of Device
• Monitoring Procedures
5 – Manufacturing Information

If you are using a marketed device, then it is appropriate to refer to the product label and provide copy or a URL to the most current product label. If any modifications have been made, provide details on all changes.

If you have a Letter of Authorization (LoA) from another sponsor referencing their FDA submission (IND, NDA, BLA, IDE, DMF, etc), include the LoA in this section.

If you are manufacturing the device, include a description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and, where appropriate, installation of the device.
6 – Investigator’s Agreement

The investigators agreement must include:

• The investigator's CV;
• If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination;
• Investigator's commitment to provide sufficient and accurate financial disclosure information.
• A statement of the investigator's commitment to:
  – Conduct the investigation in accordance with the agreement, the investigational plan, Part 812 and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB and FDA;
  – Supervise all testing of the device involving human subjects;
  – Ensure that the requirements for obtaining informed consent are met
IDE Formatting and Submission

Preface with a cover letter and include three Copies:

• One original hard copy in ACCO-like grey report cover, and

• Two electronic copies with a single cover letter that contains a signature and an adequate eCopy statement "the eCopy is an exact duplicate of the paper copy“ Or, "the eCopy is an exact duplicate of the paper copy, with the exception of..."
E-Copy details

An electronic copy (eCopy) is a PDF version of your medical device submission stored on a compact disc (CD), digital video disc (DVD), or a flash drive.

A submission with an eCopy that does not meet the technical standards outlined in the eCopy guidance will be placed on eCopy hold until a valid eCopy is received. E-Copy Guidance
Shipping Information

For devices regulated by the Center for Devices and Radiological Health (CDRH):
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

For devices regulated by the Center for Biologics Evaluation and Research (CBER):
U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center - WO71-G112
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
FDA Review

Once the initial IDE submission has been sent to the FDA, a team of staff reviews the IDE and provides one of several standard responses within 30 days of receipt.

- Acknowledgement
- Approval
- Approval with Conditions (Sponsor must reply)
- Disapproval (Sponsor must reply)
Maintaining an IDE

IDE Templates can be found at www.ReGARDD.org
Supplements / Reports / Amendments

- **Supplement** - A written response from the sponsor-investigator while IDE is under review or approved (trial is ongoing) regarding changes to the protocol or the device. Supplements are intended to seek FDA's approval for something new or different.

- **Report** – A written response from the sponsor-investigator while IDE is in effect regarding study progress and unanticipated events. Reports are intended to provide notification or updates for FDA's routine monitoring of a clinical investigation.

- **Amendment** - A written response from the sponsor-investigator in response to the FDA's request for more information regarding a previous submission.
Supplements – Prior Approval

Changes requiring prior approval - most of the time, changes that are made in the Investigational Plan, need to be pre-approved by FDA. Examples of these changes are:

• Changes in the Investigational Plan or Protocol  
  – Affecting the validity of data/information,  
  – Patient risk to benefit relationship,  
  – Scientific soundness of investigational plan,  
  – Right, safety or welfare of subjects.

• Developmental Changes in the device (including manufacturing changes) that present a significant change in design or basic principle of operation
Supplements – 5 Day Notice

Changes requiring 5-day notice - these changes do not require prior approval, but notice must be provided to FDA within 5 working days of making the change:

- Changes Effected for Emergency Use: changes in the investigational plan to protect the life or well-being of the subject in the case of emergency. However, these changes must be reported to the FDA within 5 working days.

- Non-significant changes in design or manufacturing should also be reported to the FDA within 5 working days.

- Other changes to protocol that do not fit the criteria for prior approval such as:
  - Modification to inclusion/exclusion criteria to better define the target patient population, increasing the frequency at which data or information is gathered, modifying secondary endpoints
Reports

• **Annual Progress Report**
  – Template available on [www.ReGARDD.org](http://www.ReGARDD.org)

• **Current Investigators list**
  – Report every 6 months.

• **Unanticipated Adverse Device Effects:**
  – Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (21 CFR 812.3 (s)). Report to the FDA within 10 working days.

• **Deviation from the investigational plan**
  – The investigator must notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Report to the FDA within 5 working days.
Questions?
Week 6 Evaluation Link:
https://tinyurl.com/ybs29357