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Supplemental Digital List 1

Summary of Investigational New Drug (IND) and Investigational Device Exemption (IDE) Regulations*

In the United States, the regulatory requirements governing clinical research involving investigational new drugs, biologics or devices are defined in 21 CFR 312: Investigational New Drug Application and 21 CFR 812: Investigational Device Exemptions. The sections below summarize the key elements of these regulations.

Roles and Responsibilities: Sponsors & Investigators

When an investigator files an FDA IND or IDE application to conduct a research study, they accept the role of regulatory sponsor. A **sponsor** is a person or entity responsible for the initiation and oversight of a clinical drug or device study. An **investigator** is a person responsible for the conduct of a clinical drug or device study. A **sponsor-investigator** is a person responsible for both the initiation and the conduct of a clinical drug or device study.

Regulatory Sponsor Responsibilities: Required of a sponsor, including Sponsor-Investigators:

- Notification/submissions to regulatory authority(ies)
- Delegation of duties and functions, including transfer of obligations to contract research organizations
- Medical expertise
- Trial design
- Maintaining all information on investigational products, including safety information
- Manufacturing, packaging, labeling, and coding investigational products
- Quality assurance & quality control
- Supplying ,handling and disposition of investigational products
- Investigator selection and training
- Confirmation of review by local IRBs
- Trial management, data management, and record maintenance and retention
- Adverse drug reaction/unanticipated adverse device effect reporting
- Monitoring and auditing
- Premature termination or suspension of a trial
- Management of investigator noncompliance
- Accommodating FDA auditing of the Sponsor
- Clinical trial/study reports
- Financing, including investigator and subject compensation

Investigator Responsibilities: Responsibilities required of an investigator of a clinical study:

- Ensuring investigators' qualification and agreements with the study sponsor
- Ensuring adequate resources to conduct the study
- Site-based quality assurance and quality control
- Assurance of local IRB review and approval and ongoing communication with the IRB
- Compliance with protocol, including adherence to the randomization and unblinding (unmasking) procedures
- Control of investigational product
- Informed consent of trial subjects
- Protect the rights, safety and welfare of clinical trial subjects
- Safety reporting to the sponsor and local IRB
- Progress and final reports to the sponsor and local IRB
- Premature termination or suspension of a trial
- Record maintenance and retention
- Management of site-based finances

Studies Involving Investigational Drugs

If a study involves the use of a drug that does not have FDA approval, or the research use of an FDA-approved drug that is not exempt (see section below on exemption), the investigator must submit an IND

application to the FDA to obtain permission to conduct the proposed research. The process and format for submitting an IND application is defined in § 312.23, IND Content and Format. The FDA must review the application within 30 days of formal receipt, and will either allow the IND to go into effect or place the study on clinical hold until the regulatory sponsor satisfactorily responds to all the issues raised by the FDA.

Clinical Investigations Exempt from the IND Regulations

For many investigator-initiated clinical studies, the objective of the study is to assess the use of an approved drug (or a combination of approved drugs) in a new indication, patient population or dosing regimen that is not noted in the FDA-approved drug label. This off-label use for research purposes causes the drug to be viewed as an investigational new drug from a US regulatory perspective. However, studies using FDA-approved drugs may be considered exempt from IND regulations if all of the following criteria are met [21 CFR 312.2(b)(1)]:

1. Is not intended to be reported to FDA in support of a new indication for use nor a significant change in the labeling for the drug;
2. Is not intended to support a significant change in the advertising for the product;
3. Does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
4. Is conducted in compliance with IRB review & informed consent requirements (21 CFR parts 50 & 56)
5. Is conducted in compliance with the requirements of § 312.7 - promotion & charging for investigational drugs

In cases where an IND application is submitted but the research use of the marketed drug noted in the application is considered exempt from IND regulations, the FDA issues a letter of exemption.

Studies Involving Investigational Devices

For clinical studies of investigational devices, there are two mechanisms of regulatory oversight, defined by the risk associated with use of the device. If the study involves the use of a Significant Risk (SR) device (defined in 21 CFR 812.3), then the investigator must submit an IDE application to the FDA. If the proposed research involves a Non-Significant Risk (NSR) device, and if the IRB approves the study, the study is considered to have an approved IDE that is managed by the local IRB. This is often referred to as an abbreviated IDE. In this case, the investigator obtains IRB approval after presenting the reviewing IRB with an explanation supporting his/her assertion that the device is a NSR device rather than a SR device. The IRB then decides whether or not it concurs with the investigator's NSR determination. Should the IRB disagree with the NSR rationale, the investigator is required to submit an IDE application to the FDA for formal assessment.

The process and format for submitting an IDE application is defined in 21 CFR 812.20. The FDA has 30 days from formal receipt of the application to either accept the IDE or notify the sponsor that the investigation may not begin. By initiating an investigation conducted under an FDA IDE application, the investigator assumes the responsibilities of a regulatory sponsor.

Investigational Diagnostic Devices

Clinical studies involving investigational diagnostic devices are normally exempt from the IDE regulations if such devices do not by design or intention introduce energy into a subject or are not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure. Devices that introduce energy into a subject or require an invasive sampling procedure that presents significant risk are subject to IDE regulations.

Supplemental Digital List 2

Sponsor-Investigator Support and Oversight: Points to Consider

1. **Training of the sponsor-investigator**

Investigator and research team qualifications

- Formal clinical research training of the investigator and research team members
- Prior experience of investigator in clinical research, including experience as principal investigator with clinical drug/device trials
- Availability of research mentors for investigators new to clinical research or new to drug/device research
- Education programs for faculty and research staff on regulatory requirements and specific responsibilities of IND/IDE sponsors.
- Prior clinical research experience of study coordinator, including specific experience coordinating studies for sponsor-investigators
- Existence of specific institutional requirements or qualifications permitting faculty to assume IND or IDE sponsor responsibilities

Standard operating procedures (SOPs) and SOP training programs

- Development of SOPs for sponsors of IND/IDEs with explicit processes and procedures for complying with regulations
- SOP training

2. **IND exemption determination process**

- Responsibility of central office or IRB vs. determination by individual principal investigators
- Acceptance of the determination of IND exemption made at one AHC by other AHCs for multi-site studies
- Interaction with the FDA for confirmation of AHC IND exemption determination

3. **IND/IDE application submission and maintenance support**

- Consultation services to support application process
- Contact information for specific FDA offices for IND/IDE submission
- Identification and qualification of support facilities:
  - Laboratories for preclinical research to support an IND application for a new medical entity (NME, term for newly created medical therapies not yet marketed)
- Manufacturing facilities to produce a NME investigational agent or matching placebo
- FDA interface support: meeting coordination and facilitation, maintenance of meeting notes or minutes, assistance responding to FDA requests, etc
- Templates supporting sponsor-investigator FDA submission requirements
  - Initial IND/IDE application, study protocol and cover letter
  - Investigator's Brochure (if applicable)
  - IND annual report

- Services to assist the sponsor-investigator with:
  - Maintenance of the sponsor Regulatory Master File (essential documents IND/IDE sponsors are required to maintain)
  - Creating the necessary communication plan to ensure acute safety reporting to the FDA (for serious adverse events that are unexpected and related to the study agent)
  - Construction and submission of annual FDA safety reports, required amendments and end-of-study report
  - Study site monitoring (qualification of vendors; training of internal personnel, monitoring report template)
- Data and safety monitoring plan development, including Data and Safety Monitoring Board (DSMB) Charter template
- Templates supporting compliance with Good Clinical Practice (GCP) guidelines:
  - Sponsor Regulatory Master File template
  - Site-based study administrative file (often called the "regulatory binder") template
  - Site qualification checklist
  - Investigator's brochure template
  - Manual of Operations template (the manual of operations describes the management and oversight of research sites in a multi-site research study)

4. Institutional oversight considerations

Oversight of faculty IND/IDE sponsor activities

- Database of all investigator-held IND/IDEs
- Institutional auditing of faculty IND/IDE sponsors and the associated protocols conducted under their IND/IDEs
- Qualification and training of institutional auditors of investigator-initiated IND/IDE studies
- Auditing of investigators involved in multi-site research for regulatory compliance with the responsibility to monitor study sites involved in the research
- Institutional management and reporting of any serious non-compliance encountered in the sponsor audit process (i.e. a finding of regulatory non-compliance that requires the event to be reported to the FDA)

IND/IDE ownership models

- Individual faculty as IND/IDE sponsor
- Institution as IND/IDE sponsor
- Qualifications and training of staff serving as IND/IDE sponsor (under either ownership model)

Faculty and institutional risk issues

- Defining responsible party for medical care costs for treatment of injury as a result of participation in an investigator-initiated investigational drug/device research study
- Multi-center research involving investigative sites at other institutions:
- Ensuring compliance with faculty sponsor responsibilities with increased complexity of research oversight
- Indemnification/liability issues for research injuries

5. Additional considerations

- Assistance with meeting Good Laboratory Practice (GLP) regulations for pre-clinical investigations (21 CFR 58)
- Assistance with meeting Current Good Manufacturing Practice (cGMP) regulations
  - 21 CFR 210 & 211 cGMP for drugs
  - 21 CFR 600 & 606 cGMP for biologics, blood and blood components
  - 21 CFR 820 cGMP for devices
  - 21 CFR 1271 cGMP for human cells, tissues, and cellular and tissue-based products
  - Internal or external personnel to conduct cGMP inspections of manufacturing facilities

* IND = Investigational New Drug; IDE = Investigational Device Exemption; CFR = Code of Federal Regulations; FDA = Food and Drug Administration; AHC = academic health center; SOPs = standard operating procedures; IRB = institutional review board; FDA = Food and Drug Administration; NME = new medical entity; GCP = Good Clinical Practice; GLP = Good Laboratory Practice; cGMP = current Good Manufacturing Practice.