Regulatory Issues in Human Subjects Research

Ian McNiece, PhD

University of Miami

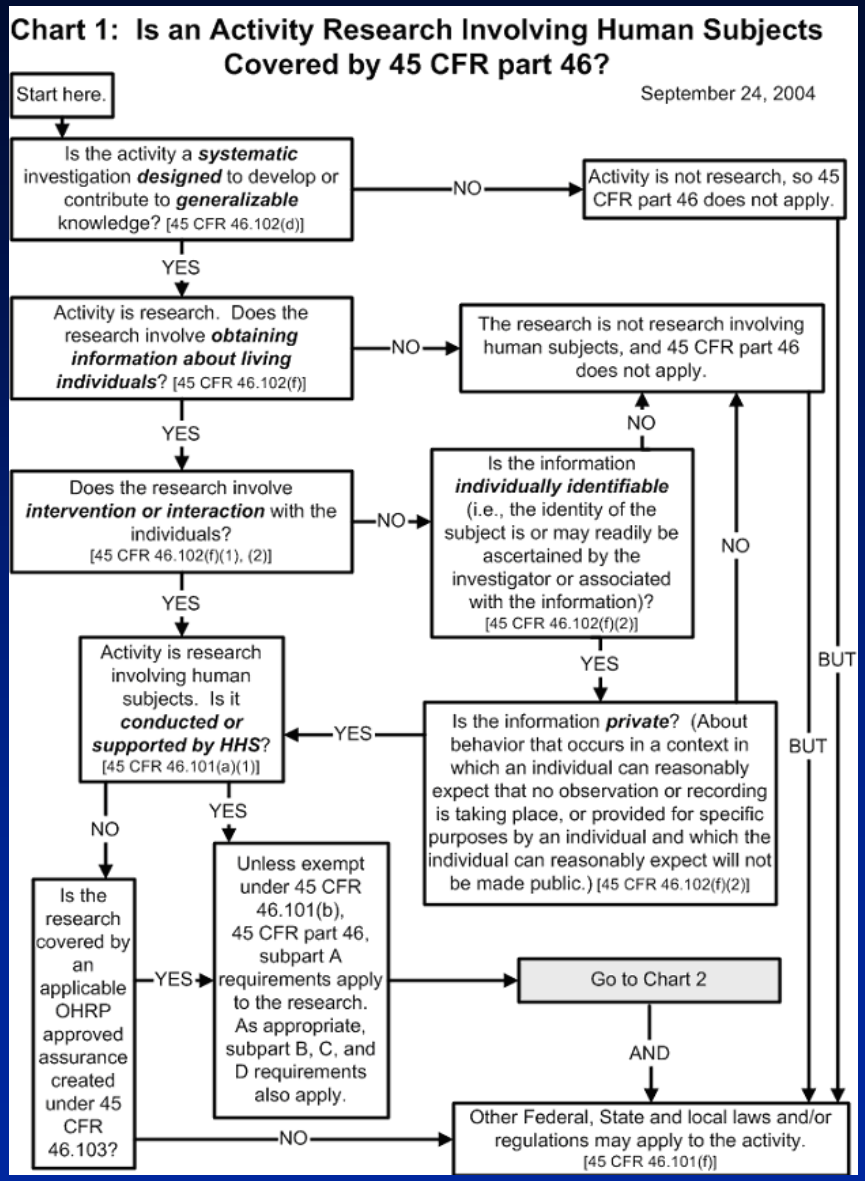
Chart 1: Is an Activity Research Involving Human Subjects Covered by 45 CFR part 46?
September 24, 2004
Start here.
Is the activity a systematic investigation designed to develop or contribute to generalizable knowledge? [45 CFR 46.102(d)]
NO
Activity is not research, so 45 CFR part 46 does not apply.
YES
Activity is research. Does the research involve obtaining information about living individuals? [45 CFR 46.102(f)]
NO
The research is not research involving human subjects, and 45 CFR part 46 does not apply.
YES
Does the research involve intervention or interaction with the individuals? [45 CFR 46.102(f)(1), (2)]
NO
Is the information individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information)? [45 CFR 46.102(f)(2)]
NO
YES
Activity is research involving human subjects. Is it conducted or supported by HHS? [45 CFR 46.101(a)(1)]
YES
Is the information private? (About behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, or provided for specific purposes by an individual and which the individual can reasonably expect will not be made public.) [45 CFR 46.102(f)(2)]
NO
YES
BUT
BUT
NO
YES
Is the research covered by an applicable OHRP approved assurance created under 45 CFR 46.103?
YES
Unless exempt under 45 CFR 46.101(b), 45 CFR part 46, subpart A requirements apply to the research. As appropriate, subpart B, C, and D requirements also apply.
Go to Chart 2
AND
NO
Other Federal, State and local laws and/or regulations may apply to the activity. [45 CFR 46.101(f)]

Human Subjects Research

- Require IRB approval
- Studies of new drugs or applications of drugs require an FDA approved IND (Investigational New Drug application)
- Studies of cellular therapies generally also require an FDA approved IND

INTRODUCTION

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

INTRODUCTION

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

INTRODUCTION

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

INDs

- There are three IND types:
- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- Emergency Use IND2 allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.233 or Sec. 312.34.4 It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- Treatment IND5 is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

- There are two IND categories:
- Commercial
- Research (non-commercial)

Investigational New Drug

- Used in clinical investigations
- Must be covered by an IND
- The regulations in 21 CFR 312 cover procedures and requirements for INDs

Sponsor

- Definition from 21 CFR 312.3(b)
- An individual, company, institution, or organization that takes responsibility for and initiates a clinical study

Sponsor

- General Responsibilities 21CFR 312.50

- Selecting qualified investigators
- Ensuring study monitoring
- Maintaining an effective IND
- Ensuring all AE risk information is provided to the FDA and investigators

Investigator

- Definition 21 CFR 312.3(b)
- An individual under whose immediate direction the study drug is administered or dispensed. If a team is involved, the leaser is the investigator; the other team members are sub-investigators

Investigator

- General responsibilities
- Ensuring the study is conducted according to the plan
- Protecting the rights, safety and welfare of subjects
- Control of drug under investigation

Sponsor-Investigator

- An individual who both inititates and conducts a study and under whose immeiate direction the study drug is administered or dispensed
- Must follow the requirements for both a sponsor and investigator

A General Principle

The FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects.

Clinical Investigation

- Any experiment in which a drug is:
  - administered to,
  - dispensed to,
  - or used involving

  One or more human subjects.

  Applies in principle to cellular products also!

Clinical Investigation

- An experiment is defined as any use of a drug except for the use of a marketed drug in the course of medical practice.
- Even FDA-licensed products are subject to IND regulations,

  if used in a clinical investigation and

  one or more of the exceptions under 21CFR312.2(b) doesn't apply.

IND Content Requirements

- Cover sheet and Form 1571
- Table of Contents
- Introductory Statement and General Investigational Plan
- Clinical Protocol
- Chemistry, Manufacturing and Control (CMC) Information
- Pharmacology and Toxicology Information
- Previous Human Experience
- Additional Information

IND Review Process

- FDA does not approve INDs
- IND is “in effect” after 30 days of submission, unless placed on clinical hold by FDA
- Clinical holds may occur at any point in the life of the IND and may affect a single study or entire IND.

Grounds for Clinical Hold

- Phase 1,2, or 3 studies:

  Unreasonable risk of harm to subjects

  Unqualified investigators

  Misleading, incomplete or erroneous investigator brochure

  Insufficient information in IND

- Phase 2 and 3 studies only:

  Plan or protocol for investigation is clearly deficient in design to meet its stated objectives

Annual Reports

- Submit within 60 days of the anniversary of “in effect” date
- Include enrollment, demographis and conduct status information
- Adverse event summaries (safety reports, deaths, dropouts)
- Drug action information
- Preclinical study status information

Human Cells, Tissues and Cellular and Tissue Based Products (HCT/Ps)

These products are covered under 21CFR Part 1271

These regulations describe requirements for establishments that manufacture HCT/Ps, donor-eligibility requirements and good tissue practices (GTPs)

Human Cells, Tissues and Cellular and Tissue Based Products (HCT/Ps)

- FDA (Center for Biologics) is responsible for the following products:
- Blood and blood products
- Cellular therapeutics
- Tissues
- Tissue engineered Products
- Xenografts
- GeneTherapies
- Vaccines

“The Tissue Rules”

- Establishments manufacturing HCT/Ps must be registered with the FDA and list products manufactured by the facility.
- Donor eligibility requires donor screening and testing for relevant communicable disease agents and diseases

Examples of HCT/Ps

- Musculoskeletal tissue
- Skin
- Ocular tissue
- Human heart valves
- Dura mater
- Reproductive tissue
- Hematopoietic stem/progenitor cells
- Other cellular therapies
- Tissue/devices and other combination therapies

Not included

- Vascularized human organs
- Minimally manipulated bone marrow
- Xenografts
- Blood products
- Secreted or extracted products; eg human milk, collagen, cell factors
- In vitro diagnostic products
- Blood vessels recovered with organs for use in organ transplantation

“361”HCT/Ps

- Regulated solely under 361 of PHS Act
- No pre-market review-no application to FDA is required
- Compliance determined at FDA inspections
- Examples – minimally manipulated cellular therapies – bone marrow for BMT

“351”HCT/Ps

- Pre-market review and approval required
  - IND/BLA – biological products
  - IND/NDA – drug
  - IDE/PMA or 510(k) - device
- Do not meet one or more criteria in 1271.10
- Pre-license/approval inspection
- Examples – cellular therapies forunrelated allogeneic use

21 CFR Part1271.10 – Criteria for Regulation Solely under 361 of the PHS Act

- Minimally manipulated
- Intended for homologous use
- Not combined with another article
- No systemic effect and not dependent on metabolic activity of living cells
  - Exceptions: autologous use; use ina first-or second-degree blood relative; or reproductive use.

IND Content Requirements

- Cover sheet and Form 1571
- Table of Contents
- Introductory Statement and General Investigational Plan
- Clinical Protocol
- Chemistry, Manufacturing and Control (CMC) Information
- Pharmacology and Toxicology Information
- Previous Human Experience
- Additional Information

TABLE OF CONTENTS – CMC

7.1 Facility Information
7.1.1 Facility Address
7.1.2 Floor Plans for the Facility
7.1.3 Organizational Chart
7.2 Location of Manufacturing and Testing
- 7.2.1 Donor Screening and Testing
- 7.2.2 Donor Collection
- 7.2.3 Cell Processing
- 7.2.3 Product Testing

7.3 Product Manufacturing – Components
- 7.3.1 Cells
  - 7.3.1.1 Cell Source
  - 7.3.1.2 Collection Methods
  - 7.3.1.3 Donor Screening and Testing
- 7.3.2 Reagents
  - 7.3.2.1 Tabulation of Reagents Used in Manufacturing
  - 7.3.2.2 Reagent Aliquoting
  - 7.3.2.3 Qualification Program
  - 7.3.2.4 Removal Method

7.4	Product Manufacturing – Procedures
7.5	Product Testing
7.5.1	Description of Test Methods & Sample Procurement
7.5.2	Release Specifications
7.6	Product Stability
7.7	Other Issues
7.7.1	Product Tracking
7.7.2	Labels
7.7.3	Container Closure System
7.7.4	Environmental Impact
7.7.5	
7.7.6	Biostatistics
7.7.7	Action Plan for Culture-Positive Products

IND Content Requirements

- Cover sheet and Form 1571
- Table of Contents
- Introductory Statement and General Investigational Plan
- Clinical Protocol
- Chemistry, Manufacturing and Control (CMC) Information
- Pharmacology and Toxicology Information
- Previous Human Experience
- Additional Information

IND Content Requirements

- Cover sheet and Form 1571
- Table of Contents
- Introductory Statement and General Investigational Plan
- Clinical Protocol
- Chemistry, Manufacturing and Control (CMC) Information
- Pharmacology and Toxicology Information
- Previous Human Experience
- Additional Information

http://www.uth.tmc.edu/ctrc/indide.html

University of Texas Health Science Center at Houston