Touring Clinical Research at MDACC

Composed by:
Lisa A. Dassler & Michelle Grogan

Tour Objectives

Able to state the purpose of frequently contacted departments within the research organizational structure of UTMDACC.

Able to locate the UTMDACC intranet resources and key personnel to answer questions about conduct of clinical research trials at UTMDACC.

Tour Spotlight: Office of Protocol Research (OPR)

Provides administrative support to the MDACC Institutional Review Board (IRB)

Call 2-2933 or e-mail IRB Help

Research Administration Information Systems (RAIS):

Protocol Document On-line (PDOL)

Call 5-PDOL for training

Protocol Data Management System (PDMS)

Call 5-PDMS for training

Clinical Oncology Research System (CORe)

Call 5-CORe for training
Tour Spotlight: Office of Research Education & Regulatory Management (ORERM)

6 major sections:
- FDA Regulatory serves as liaison & support for investigator-initiated INDs (Investigational New Drug applications)
- IND Monitoring is the monitoring component for the IND studies
- NCI Support Services serves as the liaison between UTMDACC and the National Cancer Institute (NCI)
- Tissue Banking Oversight assists with Institutional Tissue Bank initiatives
- Research Education provides training on a variety of research topics as well being responsible for the Clinical Research Training
- Auditing promotes protocol compliance

Important Resources

- Research Nurse Database
- CR Forms
- Handouts in CRT manual (notify ORERM if need larger print)
How to locate key personnel

- Keep helpline or e-mail addresses handy
- Network
- researcheducation@mdanderson.org
- 3-RSCH (3-7724)
- 3-5467 Lisa or 3-7307 Michelle
Regulations Governing Human Subjects Research
Office of Research Education and Regulatory Management

Objectives
- Identify the Federal Agencies and International Organizations that impact research at MD Anderson Cancer Center
- Describe the purpose of the Federalwide Assurance document
- Verbalize understanding that all MD Anderson Cancer Center studies are subject to the Code of Federal Regulations (CFR's)
Birth of a Regulation

Law is passed by Congress

Regulation proposed by Federal Agency and posted for public review/comment

Regulation published in Federal Register as Final Rule

Guidance Documents

- Represent “current thinking” on certain topics by the Federal agency
- Used by institutions/sponsors to develop Standard Operating Procedures

Guidances, Information Sheets, and Important Notices on Good Clinical Practice in FDA-Regulated Clinical Trials

These guidances and information sheets represent the Federal Agency's current position on a given issue and may be subject to change. They should not be used as legal agreements or be used in lieu of an official contract between the Federal Agency and the contractor. They are not intended to create, modify, or amend existing contract terms.

Firms conducting clinical trials on behalf of the Federal Agency in the United States are required to follow Good Clinical Practice (GCP) guidelines. These guidelines ensure that the trials are conducted ethically and to the highest professional standards.

Guideline and Information Sheet:

- Title: Good Clinical Practice
- Reference: Federal Agency's Good Clinical Practice Guidelines
- Effective Date: [Date]
- Revision Date: [Date]

Guidance documents are subject to change. For the most current version, please refer to the Federal Agency's official website.
You failed to conduct the studies in accordance with the investigational plan [21 CFR 312.60].
You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b)].
You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60 and 21 CFR 50].
You failed to maintain adequate records of the disposition of the drug including dates, quantity, and use by subjects [21 CFR 312.62(a)].
Title 45 (OHRP)

- The Common Rule – Protection of Human Subjects
  Part 46
  - IRB review of research
  - Informed Consent
  - Protection of vulnerable populations
    - Children
    - Prisoners
    - Pregnant women
    - Fetuses
Federalwide Assurance (FWA)

- Legally binding written document
- Commits UTMDACC to compliance with federal standards
- For ALL research regardless of funding
- Direct report between Institutional Review Board and Office of Human Research Protections
- FWA 363
Determination Letters

- Failure of IRB to review research annually
- Failure to fully inform study subjects
  - Costs associated with clinical trial
  - Study procedures
- Failure to include all required elements in ICD

DHHS

FDA

OHRP

OCR

ORI

Office of Civil Rights
Health Insurance Portability and Accountability Act (HIPAA)

- “Privacy Rule”
- Authorization for Use and Disclosure of Protected Health Information (PHI)
- Consent vs. Authorization
  - For research – May be combined into one document
- Record retention
  - Data Review studies

www.hhs.gov/ocr/privacy/
International Regulations

- International Conference on Harmonization
  - A more timely introduction of new medicinal products, and their availability to patients
  - To monitor and update harmonised technical requirements leading to a greater mutual acceptance of research and development data

www.ich.org

ICH Guidelines

The ICH topics are divided into four major categories and ICH Topic Codes are assigned according to these categories:

<table>
<thead>
<tr>
<th>G</th>
<th>E</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety Topics, i.e., those relating to clinical studies in human subjects (Dose Response Studies, Good Clinical Practices, etc.)</td>
<td>Efficacy Topics, i.e., those relating to clinical studies in human subjects (Dose Response Studies, Good Clinical Practices, etc.)</td>
<td></td>
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</tbody>
</table>

ICH GCP Guidelines

- Efficacy Topics
  - E6 Good Clinical Practice Guidelines
  - E2A Clinical Safety Data Management
  - E8 General Considerations for Clinical Trials
Research Ethics and the IRB

Richard L. Theriault, D.O., F.A.C.P.
Chair, Institutional Review Board

Definition of Ethics

Merriam-Webster’s Collegiate Dictionary
1. The discipline dealing with what is good and bad and with moral duty and obligation
2. A set of moral principles or values
3. A theory or system of moral values

Definition of Ethics

• “Formal, systematic, critical analysis of rightness and wrongness of human actions”
  – Edmund Pellegrino, M.D., M.A. C.P.
  • Chairman of the President’s council on Bioethics
Definition of Research

- Research is designated as an activity that permits conclusions to be drawn, and develops or contributes to generalizable knowledge.

Research Activities

- Research may involve direct interactions or interventions with subjects for the purpose of gaining generalizable information.
- Research may also involve indirect activities such as the analysis of specimens or data from people.
- Both are Human Subjects research subject to Federal Regulation

“Why discuss ethics and research?”
Scientific Misconduct

“Fabrication, falsification, or plagiarism in proposing, performing or reviewing research, or in reporting research results.”

Recent Ethical Questions in Research

- “Is placebo surgery unethical?”
- “More questions about research misconduct”
  Science 2002; 297:13

“Trust is a shared value of science”

Donald Kennedy
Editor-in-chief
Science
Trust

• Trust “bank account”
• Hard to save
• Easy to spend
• Once “lost” difficult to “find”

“Always do right. This will gratify some people, and astonish the rest”

Mark Twain

Scientific Misconduct

Texas Scientist Admits Falsifying Results

Science 290:245, 2000
Laboratory Science
Scientific Misconduct

University Fires Bezwoda for Scientific Misconduct

The Cancer Letter 25:4-6, 2000

Clinical Science

Something Missing?

“Conscience: the inner voice that warns us that someone may be looking”

H.L. Mencken

Clinical Research

• The application of research in human beings
• Ethical issues
  – informed consent
  – subject selection
  – use of placebos
  – risk benefit ratios and determination of appropriateness
  – value of research to society
  – research in developing countries

Ultimate Purpose - help suffering humanity
“There is a general rule, and I have seen great physicians acting on it, that the physician should not treat the disease but the patient who is suffering from it”

Maimonides (1135-1204)

Is there an inherent conflict in clinical research - patient care vs. research?

Clinical Research and Clinical Care

- Clinical care based ethically on individual patient well being and “best interests”
- Clinical research based ethically on developing new knowledge not individual patient well being and “best interests”


Is research “risky”?
“Life is short, the art is long, opportunity fleeting, experiment treacherous, judgment difficult”.

First Aphorism of Hippocrates

Human Subjects Research
Ethical Guidelines

<table>
<thead>
<tr>
<th>Date and Revisions</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>1947</td>
<td>Nuremburg Code</td>
</tr>
<tr>
<td>1979</td>
<td>Belmont Report</td>
</tr>
</tbody>
</table>

The Nuremberg Code
August 1947
(1st International Standard)

- Informed consent from “volunteers” without “coercion”
- Human experiments based on prior animal experimentation
- Anticipated results should justify experiment
- Only qualified scientists should conduct medical research
- Physical and mental suffering and injury should be avoided
- Should be no expectation of death or disabling injury from the experiment
Research War Crimes

1946 - 23 Nazi physicians tried because of “research atrocities”

Research War Crimes

• High-altitude experiments
• Freezing experiments
• Sea-water experiments

Research
USA - 1946
Harvard University
Massachusetts Institute of Technology

• Researchers covertly fed radioactive iron and calcium to boys at Fernald State School to study the ability to digest minerals

Is this ethical?
The Willowbrook Study
1963
• New York Willowbrook State School Children deliberately infected with hepatitis virus
  – fed extracts from stools of infected individuals
  – injected with virus preparations
  – There was informed consent
    Is this ethical?

Jewish Chronic Disease Hospital - New York
1963
• Live cancer cells injected into hospitalized patients
• Patients not told because
  “this would frighten the patients unnecessarily”

Declaration of Helsinki - 1964

Twelve Basic Principles
• Purpose of biomedical research defined
  – Improve diagnostic, therapeutic and prophylactic procedures
  – Improve the understanding of the etiology and pathogenesis of disease
  – Goal: “Help suffering humanity”
  – Clinical research defined –
    “Medical research combined with professional care”
The Declaration of Helsinki

Broader in scope than the Nuremberg Code. Included items such as:

• Research must conform to:
  – generally accepted scientific principles (GASP)
  – Based on performed laboratory and animal experimentation
  – Based on a thorough knowledge of the scientific literature

The Declaration of Helsinki

• The right of the research subject to safeguard his or her integrity must always be respected
• In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail

Background for Clinical Research Ethics
United States

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1953</td>
<td>NIH requires panels of scientists to review protocol studies involving healthy volunteers</td>
</tr>
<tr>
<td>1962</td>
<td>Food, Drug, Cosmetic Act amended; requires patients be informed and give consent to the use of &quot;experimental&quot; drugs precipitated by thalidomide</td>
</tr>
<tr>
<td>1962</td>
<td>Kefauver-Harris drug amendments; drug manufacturers required to prove to FDA product effectiveness before marketing</td>
</tr>
</tbody>
</table>
Thalidomide Review

• Frances Oldham Kelsey, M. D., Ph D.
  – Refused rapid approval of thalidomide
  – 10,000 children in 46 countries with deformities due to thalidomide
  – Kelsey received the Distinguished Federal Civilian Service medal August 1962
  – Inducted into the National women’s Hall fo Fame October 2000

Background for Clinical Research Ethics United States

<table>
<thead>
<tr>
<th>1966</th>
<th>Dr. Henry K. Beecher reported in New England Journal of Medicine 22 studies with serious ethical problems.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study design</td>
</tr>
<tr>
<td></td>
<td>Informed consent</td>
</tr>
</tbody>
</table>

Unethical Research USA Tuskegee Study

• Natural history of syphilis (1932-1972)
• Conducted by U.S. Public Health Service
  – 400 black men with syphilis, 200 controls
  – no informed consent
  – lied about “special treatment” spinal taps
• By 1946 death rate known to be 100% higher for untreated disease
• None offered penicillin when it had been shown to be curative in 1940s

*vulnerable population
Tuskegee - Public Knowledge

- Published by Jean Heller in New York Times Washington Star July 25, 1972
- Lead to the National Research Act 1974

U.S. Congress – The Research Act of 1974

- Established IRB's to review all research funded by Department of Health and Welfare
- Established "National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research"

The Belmont Report - April 1979

- Issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Three basic principles
- Governs all research supported by U.S. Government, including NIH intramural research
The Belmont Report

The Belmont Report included:
• Criteria for distinguishing research from the practice of medicine
• Delineated how to apply the general principles to the conduct of research

Principles Approach to Ethics

• Autonomy
• Beneficence/non-maleficence
• Justice

— The Belmont Report 1979

Autonomy

• Derived from Greek autos (self) and nomos (rule)
• Assumes a person is free from controlling influences and limitations
• Requires liberty and capacity for intentional action
• Capacity Assessment Essentials
  — Neurological status
  — Judgment status
  — Understanding of clinical situation
  — Explanation of decision in logical manner
  — Decision stable over time
Beneficence

- A moral obligation to act for the benefit of others
- "Do good and be kind"
  - One ought to prevent evil or harm
  - One ought to remove evil or harm
  - One ought to do or promote good

*Principles of Biomedical Ethics*
Tom Beauchamp and James Childress, 5th ed

Non-Maleficence

- One ought not to inflict evil or harm
- Generally the “do nots”
  - Do not kill
  - Do not injure
  - Do not violate
  - Do not cause pain and suffering
  - Do not cause offense

*Principles of Biomedical Ethics*
Tom Beauchamp and James Childress 5th ed

Justice

- Aristotle – “Equals must be treated equally and un-equals must be treated unequally”
- Fair access and protection from exploitation*

*Principles of Biomedical Ethics*
Tom Beauchamp and James Childress 5th ed
**Question for IRB?**

“What makes clinical research ethical?”*

- Social or scientific value
- Scientific validity
- Fair subject selection
- Favorable risk - benefit ratio
- Independent review
- Informed consent
- Respect for potential and enrolled subjects

*E. Emmanuel et al JAMA 2000, 283:2701-2711

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**Social or Scientific Value**

- Research evaluation of process, procedure, intervention that could lead to improvements in health or well-being or increase knowledge
- Society must gain knowledge
- Assumes a substantial hypothesis is being tested

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**Scientific Validity**

- Rigorous methodology
- Practically feasible
- Clear objective
- Sufficient power to test the objective
- Appropriate plan for data analysis
- Possible to complete the study
- Must have “an honest null hypothesis”
- “Clinical equipoise”
- If there is a clear consensus about better or best treatment research is invalid
Clinical Equipoise

• “a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial”
• Benjamin Freedman, Ph.D.

Clinical Equipoise - Another View

• “The ethics of research and of therapy are fundamentally different, and clinical equipoise should be abandoned”

Miller FG and Brody H. Hastings Center Report 2003;33:19-28

Fair Subject Selection

• Inclusion criteria
• Exclusion criteria
• Subject pool and recruitment
• Age, race, sex, social position, finances, vulnerable populations - special considerations
• Selection - minimize risks, enhance individual and societal benefit
Favorable Risk - Benefit Ratio  
(beneficence and nonmaleficence)

- Potential risks are minimized  
- Potential benefits enhanced  
- Potential benefits to individual and society are proportionate to or outweigh the risks

For the Participant

Potential benefits enhanced

- Potential benefits to individual and society are proportionate to or outweigh the risks

Independent Review

- Minimize impact of extant or possible conflicts of interest  
- Social accountability  
- Requires a committee  
  - broad expertise  
  - empowered to approve, amend, defer, disapprove or terminate clinical studies

Informed Consent  
(Respect for Persons) (Autonomy)

Purpose - ensure that individuals control their participation in research:
- ensure individuals participate only when research is consistent with their values, preferences, and interests  
- Personal culture of the research subject
Personal Culture – Research Subject

• Place of birth
• Family
• Religion
• Education – schooling
• Friends
• Activities
• Life experiences

Respect for Potential and Enrolled Subjects

• Privacy of individuals must be safeguarded
• Individuals may withdraw from research without penalty
• New information must be provided as learned
• Individual’s welfare must be continuously monitored
• A mechanism must be assured to inform participants of research results

The Modern Clinical Research Scientist

“The doctor should be well mannered, bold yet cautious, and should abhor false cures or practices. He should be affable to the sick, kind hearted to his colleagues, and wise in his prognostications. He should be chaste, sober, compassionate and merciful”.

Guy de Chauliac (1290-1370)
Human Subject Protection
Institutional Review Board (IRB)

- IRB
  - Committee designated by an institution to:
    Review and approve the initiation of biomedical research involving human subjects in accordance with FDA and OHRP regulations.

Institutional Review Board (IRB)

- Protect the rights and welfare of human subject
- Accountability to HHS via FDA, OHRP

Purpose of IRB Review

- Risk to subjects are minimized
- Evaluating risks (harms) vs. benefits
- Selection of subjects equitable
- Informed consent - sought from each prospective subject or legal representative
- Monitoring data collected to ensure safety of subjects
- Protect privacy and confidentiality of subjects
- Safeguard welfare of vulnerable groups
Continuing Review of Research by IRBs

- Continued review of research ≤ 1 year intervals
  - Risks (AE)
  - Changes in research - Amendments to protocol
  - New risks
  - Ensure safety of subjects
  - Must be written review
  - Authority to suspend, terminate or continue research

Investigators’ Requirements

Necessary expertise
- methodology
- statistics
- outcome measures
- scientific background
- ethical background
- conduct and supervision of trial
- analysis and reporting of trial results

Investigators Responsibilities

- Follow the protocol
- Submit research to the IRB and have approval prior to initiation of research
- Comply with IRB policies, decisions, conditions, and requirements
- Obtain and document informed consent
- Provide a copy of the IRB approved consent form to each subject
- Ensure that assent is obtained from research participants who are minors (18 years of age and under)
Investigators Responsibilities

- Report progress of approved research annually
- Submit any modifications to a protocol or consent form
- Maintain a protocol file

OHRP Authorization
Code of Federal Regulations Part 46
- Protection of Human Subjects (45CFR46)
- Revised regulations for the conduct of research
- Defines the IRB
  - What
  - Who – must be 5 members minimum, 1 public
  - How (functions, operations, method of research review)
  - When and how often
  - Provides requirements for informed consent

FDA Authorization
Code of Federal Regulations part 21
- CFR Part 21
  - Regulates new drug development
  - Regulates new device development
Enforcement of CFR

- Department of U.S. Health and Human Services
- Office for Human Research Protections (OHRP)
- U.S. Food and Drug Administration

ohrp.osophs.dhhs.gov/
www.fda.gov/oc/gcp/default.htm
select Policy Guidance

“Declare the past, diagnose the present, foretell the future. As to diseases; make a habit of two things - to help and not to harm”

Epidemics I - Hippocrates*

*attributed
Scientific Integrity

Office of Research Education and Regulatory Management

Objectives
- Identify who is subject to the UTMDACC Scientific Integrity Policy
- Identify behaviors which constitute scientific misconduct
- State the role of the Research Integrity Officer

"The public will support science only if it can trust the scientists and institutions that conduct research."

- Integrity in Scientific Research: Creating an Environment That Promotes Responsible Conduct, Institute of Medicine 2002.
For Science's Gatekeepers, a Credibility Gap

By LAWRENCE K. ALTMAN, M.D.

Published: May 2, 2006

What's Being Done?

In March 1989, congress passed section 493 to the Public Health Service (PHS) Act which created the Office of Scientific Integrity (OSI) and the Office of Scientific Integrity Review (OSIR).

The sole purpose of these offices was to deal with scientific misconduct.

What's Being Done?

In May 1992, OSI and OSIR were consolidated into one office that is known today as the Office of Research Integrity (ORI). ORI is an independent entity within the Department of Health and Human Services (HHS).
What the Office of Research Integrity Does

- Implemetns PHS regulations requiring institutions to respond to allegations of scientific misconduct
- Assures institutions requesting PHS funds have mechanisms in place to deal with allegations of scientific misconduct
- Provides assistance and guidance to institutions
- Can perform own investigation
- Leaves primary responsibility with individual institutions

RESEARCH MISCONDUCT POLICY

PURPOSE

The purpose of this policy is to establish and communicate research misconduct guidelines for individuals involved in research activities at The University of Texas M. D. Anderson Cancer Center (M. D. Anderson).

POLICY STATEMENT

It is the policy of M. D. Anderson to foster a research environment that:

- Promotes the responsible conduct of research, research training, and activities related to that research or research training.
- Discourages research misconduct, and
- Deals promptly with allegations or evidence of possible research misconduct.

Research Misconduct

42 CFR Part 93

- Fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results
- Does not include honest error or differences in opinion.
Fabrication

- Making up data or results and recording or reporting them

Allyn M. Norman, DO
North Forest Medical Associates
Getzville, NY

- Enrolled 7 fictitious subjects into an osteoarthritis study
- Forged informed consent and case report forms
- Fabricated telephone contact information with subjects
- Substituted subject blood and urine for samples from surplus

Allyn M. Norman, DO cont.

- Failed to conduct the study according to the approved protocol
- Never administered study drug to any subject but destroyed it on site
- License suspension for 3 yrs, fined $5000, and required education
- FDA Disqualified October 2003
Plagiarism

- Appropriation of another person's ideas, processes, results, or words without giving appropriate credit

Falsification

- Manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.

Types of Data Falsified

- EKGs
- Vital Signs
- Physical exams
- Lab specimens
- Subject identities
- Drug accountability and compliance records
- Informed consent
Paul H. Kornak

- Iron and Atherosclerosis Study
- Tax 325 for Gastric Cancer
- Tax 325 for Prostate Cancer
- NCI Bladder Cancer Study

The New York Times
In Harm’s Way - Abuses Endangered Veterans in Cancer Drug Experiments
February 6, 2005

Requirements for Finding of Misconduct

- Significant departure from accepted practices of research community
- Committed intentionally, knowingly, or recklessly
- Must be proven by preponderance of the evidence

Vickie L. Hanneken, R.N.
former Clinical Research Associate

- Fabrication of laboratory reports on 2 participants
- Falsification of the physician’s and nurse’s records for 10 participants
- Fabrication of the nurse’s records for 2 participants
- Falsification of patients’ history and physical forms for 21 participants
- Falsified data into the SWOG computerized data base for 13 participants
Fabricated interview data for at least 50 interviews of human subjects enrolled in the Maine Evaluation of Consumer-Operated Services Project for mental health services.

The project had to nullify all 346 interviews due to her involvement at one or more stages with the subjects.

What do you do if you suspect research misconduct?

Allegations are reported to:
- Department Chair
- Division Head
- Vice President
- Provost and Executive Vice President
- Institutional Integrity Officer
- Compliance Officer

Research Integrity Officer

The institutional official responsible for assessing allegations of scientific misconduct and determining when such allegations warrant inquiries and for overseeing inquiries and investigations.
Allegation

\[ \rightarrow \]

Inquiry  $\Rightarrow$ Insufficient evidence – No further action

\[ \rightarrow \]

Investigation

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**Inquiry**

- Purpose is to conduct an initial review of the evidence to determine whether to conduct an Investigation
- Must be completed within 60 days

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**Research Records**

- Obtain custody of all the Research Records and evidence needed to conduct the Research Misconduct Proceedings
- Inventory the records and evidence
- Sequester the records and evidence in a secure manner
Investigation
- Must begin within 30 Days
- Notice to the Office of Research Integrity
- Notice to the Respondent
- Custody of the records
- Three committee members from the Faculty Senate will evaluate the evidence
- Draft Investigation Report

42 CFR 93.310

Investigation
- Respondent copy
- Respondent opportunity to comment
- Institutional Investigation Report
  - Statement of findings
  - Did misconduct occur or not
- Must be completed within 120 days

42 CFR 93.310

Notice to ORI
- Investigation Report
- Final Institutional Action
- Findings
- Institutional Administrative Actions

42 CRF 93.316
Office of Research Integrity

After completing its review, ORI may:

- Close the case if ORI decides that research misconduct did not occur
- Make findings of research misconduct and make settlement recommendations to HHS
- Propose and obtain HHS approval of administrative actions based upon the institution's records and any other information obtained during the ORI review

http://ori.hhs.gov

36 PHS Administrative Actions – ORI website

- No PHS Funds (N=25)
  ~2 years to lifetime
- Retractions or Corrections to Publications (N=4)
- Prohibited from serving in advisory capacity to PHS 3 years to lifetime (N=36)
- Supervision and/or Certification Plans (N=7)
  ~3 to 5 years
HHS Administrative Actions

References

- 42 CRF Part 93 Public Health Service Policies on Research Misconduct
- Office of Research Integrity website: http://ori.hss.gov
Information Sheet Guidance
For IRBs, Clinical Investigators, and Sponsors

FDA Inspections of Clinical Investigators

Additional copies are available from:

Good Clinical Practice Program, HF-34
Office of Science & Health Coordination, Office of the Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) (301)-827-3340
http://www.fda.gov/oc/gcp/guidance.html

U.S. Department of Health and Human Services
Food and Drug Administration

January 2006
Information Sheet Guidance
For IRBs, Clinical Investigators, and Sponsors
FDA Inspections of Clinical Investigators

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to provide information about FDA inspections of clinical investigators conducted under FDA’s Bioresearch Monitoring (BIMO) Program. This document supersedes another document, "FDA Clinical Investigator Inspections," issued in September 1998, by the former Office of Health Affairs, FDA. This document has been revised to provide updated information and is being issued in accordance with the Agency’s regulations on Good Guidance Practices (21 CFR 10.115).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA developed its BIMO Program to ensure the protection of the rights, safety, and welfare of human research subjects and the quality and integrity of data submitted to the Agency. Among

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1 This guidance document was developed by the Good Clinical Practice Program in the Office of the Commissioner (OC) in coordination with the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Office of Regulatory Affairs (ORA).

other things, the FDA BIMO Program involves site visits to clinical investigators, sponsors, monitors, contract research organizations, Institutional Review Boards (IRBs), nonclinical (animal) laboratories, and bioequivalence analytical laboratories. This document addresses site visits to clinical investigators who conduct clinical investigations that are regulated by FDA under 21 USC 355(i) and 21 USC 360(j) and clinical investigations that support applications for research or marketing permits for products regulated by FDA.

III. WHEN ARE CLINICAL INVESTIGATOR INSPECTIONS CONDUCTED?

FDA conducts clinical investigator inspections to determine if the clinical investigators are operating in compliance with current FDA regulations and statutory requirements. Clinical investigators who conduct FDA regulated clinical investigations are required to permit FDA investigators to access, copy, and verify any records or reports made by the clinical investigator with regard to the disposition of the product and subject case histories (21 CFR 312.68 and 812.145). FDA personnel typically perform this oversight function through on-site inspections designed to document how the study was actually conducted at the clinical investigator’s site. Clinical investigators are required to retain records for a period of two years following the date a marketing application is approved for the product or, if no application is filed or if the application is not approved, until two years after the investigation is discontinued and FDA is notified. (See 21 CFR 312.62(c) and 812.140.) FDA conducts both announced and unannounced inspections of clinical investigator sites:

- routinely to verify data that has been submitted to the Agency;
- as a result of a complaint to the Agency about the conduct of the study at the site;
- in response to sponsor concerns or termination of the clinical site;
- at the request of an FDA review division; and
- related to certain classes of investigational products that FDA has identified as products of special interest in its current work plan (i.e. targeted inspections based on current public health issues).

IV. HOW ARE CLINICAL INVESTIGATOR INSPECTIONS CONDUCTED?

During an inspection at the site of a clinical investigator, FDA personnel typically verify:

- who performed various aspects of the protocol (e.g., who verified inclusion and exclusion criteria, who obtained informed consent, who collected adverse event data);
- the degree of delegation of authority (e.g., how the clinical investigator supervised the conduct of the investigation);
- where specific aspects of the investigation were performed;
- how and where data were recorded;
- accountability for the investigational product;
- the monitor's communications with the clinical investigator; and
- the monitor's evaluations of the progress of the investigation.
FDA personnel also audit the study data by comparing the data filed with the Agency or the sponsor, if available, with records related to the clinical investigation. Such records include the case report forms and supporting data including signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. FDA may also examine medical records about the subjects that predate the study to find out whether the condition under study was in fact diagnosed, the study eligibility criteria were met, and whether the subject received a possibly interfering medication before the investigation began. FDA personnel also review subjects' records covering a reasonable period after completion of the product-related portion of the investigation to determine if there was proper follow-up as outlined in the protocol, and if the clinical investigator reported all signs and symptoms reasonably attributable to the product's use.

V. WHAT HAPPENS AFTER AN INSPECTION?

At the end of an inspection, FDA personnel conduct an exit interview with the clinical investigator or his/her representative. At this interview, FDA personnel who conducted the inspection review and discuss the findings from the inspection and if deficiencies are found, issue a written Form FDA 483 (Inspectional Observations; 483) to the clinical investigator or his/her representative. The 483 describes any inspectional observations that, in the opinion of the FDA personnel conducting the inspection, represent deviations from applicable statutes and regulations. The clinical investigator may respond to the 483 observations verbally during the exit interview and/or respond in writing after the inspection. If the clinical investigator chooses to respond in writing to the deficiencies listed on the 483, the response should be directed to the FDA District Office listed in the upper left corner of the 483. (A list of FDA District Offices is also posted on FDA's website (http://www.fda.gov/ora).

Following the inspection, the FDA personnel who conducted the clinical investigator inspection prepare a written Establishment Inspection Report (EIR). The EIR, 483 (if issued), copies of any materials collected during the inspection, and any clinical investigator response are forwarded to the appropriate FDA Center for further evaluation. After this review, one of the following types of letters is typically sent from the Center to the clinical investigator:

1. A letter that generally states that FDA observed no significant deviations from the regulations. Note that a letter is not always sent when FDA observes no significant deviations.

2. An informational or untitled letter that identifies deviations from statutes and regulations for which voluntary corrective action is sufficient. Occasionally, such letters request a response from the clinical investigator.

3. A Warning Letter that identifies serious deviations from applicable statutes and regulations. A Warning Letter generally requests prompt correction by the clinical investigator and a formal written response to the agency.
Please note that FDA may disclose to sponsors and IRBs records that indicate a violation or potential violation of the law by clinical investigators that have conducted or are conducting studies.³

In addition to issuing these letters, FDA can take other administrative action against clinical investigators for non-compliance with applicable statutes and regulations. For example, FDA may initiate a process to disqualify the clinical investigator from receiving investigational products in the future if the investigator has repeatedly or deliberately failed to comply with applicable statutory or regulatory requirements or has submitted false information to the sponsor or FDA in any required report. (See § 312.70, § 812.119.)

VI. WHO CAN PROVIDE MORE INFORMATION?

If, during an FDA inspection, a clinical investigator has any questions that the FDA personnel conducting the inspection has not answered, either the District Office Director or the contact person at the Center that assigned the inspection can be contacted. The FDA personnel conducting the inspection should be able to provide the name and telephone number of the District Office Director and the specific Center contact person.

In addition, the FDA Compliance Program Guidance Manual for Clinical Investigator Inspections (Program 7348.811), used by FDA to conduct these inspections, is available on the Internet at http://www.fda.gov/ora/cpgm/default.htm#bimo.

³ See 63 FR 55873, October 19, 1998.
<table>
<thead>
<tr>
<th>2. NAME AND TITLE OF INDIVIDUAL</th>
<th>3. DATE</th>
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<td>4. FIRM NAME</td>
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<td>TO</td>
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<td>6. NUMBER AND STREET</td>
<td>p.m.</td>
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<tr>
<td>7. CITY AND STATE &amp; ZIP CODE</td>
<td>8. PHONE &amp; AREA CODE</td>
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1. DISTRICT OFFICE ADDRESS & PHONE NO.

<table>
<thead>
<tr>
<th>9. SIGNATURE (Food and Drug Administration Employee(s))</th>
<th>10. TYPE OR PRINT NAME AND TITLE (FDA Employee(s))</th>
</tr>
</thead>
</table>

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetics Act [21 U.S.C. 374(a)] and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264].

1. Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:

Sec. 704. (a)(1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for the purpose of examining, upon request, by the persons to whom such regulation or order is applicable, of similar information received or otherwise obtained by the Secretary.

Sec. 704(e) Every person required under section 714 to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee duly designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

2. Applicable sections of Parts F and G of Title III Public Health Service Act [42 U.S.C. 262-264] are quoted below:

Part F - Licensing - Biological Products and Clinical Laboratories and*****

Sec. 351(c) "Any officer, agent, or employee of the Department of Health & Human Services, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the purpose of examining, upon request, by the persons to whom such regulation or order is applicable, of similar information received or otherwise obtained by the Secretary.

Sec. 351(c) "Any officer, agent, or employee of the Department of Health & Human Services, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the purpose of examining, upon request, by the persons to whom such regulation or order is applicable, of similar information received or otherwise obtained by the Secretary.

Form FDA 482 (9/00) PREVIOUS EDITION IS OBSOLETE

(Continued on Reverse)
(f) "The Secretary may by regulation (1) require dealers and distributors of electronic products, to which there are applicable standards prescribed under this subpart and the retail prices of which is not less than $50, to furnish manufacturers of such products such information as may be necessary to identify and locate, for purposes of section 359, the first purchasers of such products for purposes other than resale, and (2) require manufacturers to preserve such information. Any regulation establishing a requirement pursuant to clause (1) of the preceding sentence shall (A) authorize such dealers and distributors to elect, in lieu of immediately furnishing such information to the manufacturer to hold and preserve such information until advised by the manufacturer or Secretary that such information is needed by the manufacturer for purposes of section 359, and (B) provide that the dealer or distributor shall, upon making such election, give prompt notice of such election (together with information identifying the notifier and the product) to the manufacturer and shall, when advised by the manufacturer or Secretary, of the need therefor for the purposes of Section 359, immediately furnish the manufacturer with the required information. If a dealer or distributor discontinues the dealing in or distribution of electronic products, he shall turn the information over to the manufacturer. Any manufacturer receiving information pursuant to this subsection concerning first purchasers of products for purposes other than resale shall treat it as confidential and may use it only if necessary for the purpose of notifying persons pursuant to section 359(a)."

Sec. 360 B. (a) It shall be unlawful-
(1) ***
(2) ***
(3) "for any person to fail or to refuse to establish or maintain records required by this subpart or to permit access by the Secretary or any of his duly authorized representatives to, or the copying of, such records, or to permit entry or inspection, as required or pursuant to section 360A."

***

Part G - Quarantine and Inspection

Sec. 361(a) "The Surgeon General, with the approval of the Secretary, is authorized to make and enforce such regulations as in his judgement are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession. For purposes of carrying out and enforcing such regulations, the Surgeon General may provide for such inspection, fumigation, disinfection, sanitation, pest extermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, as in his judgement may be necessary."
The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides: “Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary.”
Investigational New Drugs

Chicquita Hatten, RN, MSN, CCRC, CCRA
Manager, IND Office, ORERM

Objectives

• Define IND
• Determine when is an IND required
• Identify Institutional IND Resources
• Verbalize understanding of the institution’s role as IND Sponsor
• Describe the PI Override process
• Identify the steps and resources for Compassionate Use IND

IND – Investigational New Drug

…a new drug, antibiotic drug, or biological drug that is used in a clinical investigation. 21 CFR 312

IND Required:
• For agents that are not commercially available
• For agents that are commercially available used in a way that may increase risk
Criteria for IND Exemption

- Agent must be commercially available
- No change in label
- No change in advertising
- No factors that significantly increase the risk over the approved use.

What is “increased risk”?

- Cytotoxic therapy for non-cancer use
- Studies of adjuvant chemotherapy
- New agent substituted for a proven therapy
- Initial studies of new combinations

What is “increased risk”?

- Initial studies of new routes or schedules – not described in the literature
- Initial studies of agents meant to be chemosensitizers, radiosensitizers, or resistance modulators

http://www.fda.gov/cber/gdins/indcancer.htm
Types of Initial IND Submissions

- Original application includes all pre-clinical data and all proprietary info
- Cross filed application includes protocol, PI’s CV and letter from sponsor of original application for FDA to reference the original IND

IND Submission

- Cover sheet (Form FDA-1571)
- Table of contents
- Investigator’s brochure
- Protocols
  - Chemistry, Manufacturing & Control Info
  - Pharmacology & Toxicology Info
  - Previous Human Experience
  - Other additional & Relevant Information

FDA IND Approval Process

- Submit IND packet in triplicate
- FDA letter of receipt is generated
- FDA has 30 days to review
- Does treatment plan allow safety and efficacy to be determined?
- Request additional information
- Impose clinical hold
IND Sponsor

Who is the IND Sponsor?

• Submits the IND application to FDA
• Communicates with FDA about IND
• Accepts liability related to conduct of study

UTMDACC INDs

At M. D. Anderson the Institution rather than the investigator is the IND sponsor.

Key Points – MDACC INDs

• Only MDACC faculty participate under MDACC INDs
• Difficulty to meet sponsor responsibilities at other sites
• Patients must receive their treatment here
• Contact a Project Manager in the IND office for IND Application and information
Key Points

- All communication with federal agencies must be coordinated through the Project Manager (IND Office).
- Pre-IND tele-conference
- Initial submission
- Continued support throughout the life of the trial

Continued Support

- Protocol Revisions
- Serious Adverse Events
- IND annual reports
- Informational Amendments
- Protocol Specific Questions
- Submissions to IBC and NIH/RAC

NIH Guidelines

The NIH Guidelines for Research Involving Recombinant DNA Molecules

- Specific practices for constructing and handling rDNA molecules and organisms and viruses containing DNA
- Appendix M
- Institutional Biosafety Committee
Compassionate Use of Investigational Drugs (CIND)

MDACC term for authorization to treat single patient
• Provided out of compassion for the patient’s need
• Not a mechanism for conducting clinical research
• Patient information may not be included in protocol data analysis

When should a CIND be submitted?

• Subject does not meet eligibility criteria for any currently open protocols
• A drug or medical device is not currently approved for treatment.
• The drug will be administered through new route of administration or at novel dose level (commercially available).

“Off-Label” use of marketed drugs, biologics and medical devices

Use of a marketed product not in the approved labeling, but with intent to practice medicine, and in the best interests of the patient (with firm scientific rationale, sound medical evidence, good medical practice) does not require CIND.
PI Override

Minor eligibility deviation from existing open protocol that will not effect integrity or analysis of study results

PI Override vs. CIND

<table>
<thead>
<tr>
<th>Indications for Use</th>
<th>Informed Consent</th>
<th>Protocol Number</th>
<th>Data Analysis</th>
<th>Signatures on Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI override</td>
<td>Pt signs protocol consent form</td>
<td>Pt will be registered under existing protocol number</td>
<td>Pt may include pt information in the analysis of protocol data</td>
<td>Treating MD, PI, IRB Chair/Vice Chair</td>
</tr>
<tr>
<td>CIND</td>
<td>Have pt sign CIND consent form</td>
<td>Pt will be registered on a CIND protocol</td>
<td>Pt may not include CIND pt information in the analysis of the referenced protocol</td>
<td>Treating MD, Department or Division Head, VP of Clinical Research</td>
</tr>
</tbody>
</table>

References

IND
-21CFR 312.32

CIND
-Human Subjects Research Manual –Chapter 16
-Clinical Research Forms – 1.003

PI Override
-Clinical Research Forms – 1.101
Contact Information

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• Fax 713-563-5468
• cjhatten@mdanderson.org