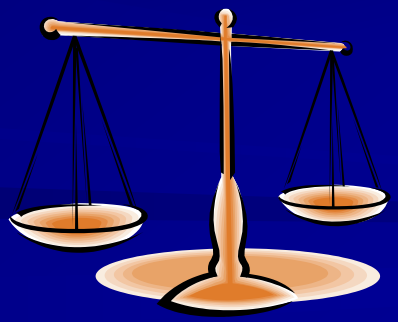
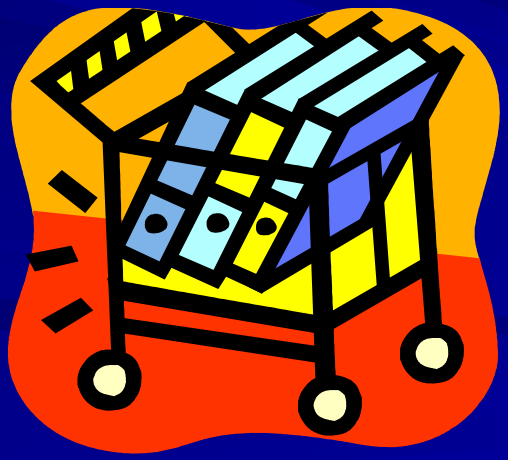
FDA CFR Title 21

United States
Code of Federal Regulations (CFR)

- Compliance to the CFR is required for projects run globally when the data from those projects will be submitted under a US IND Application unless regional regulations supersede or have supplemental requirements



Investigational New Drug Application
21 CFR Part 312



Investigational New Drug Application
21 CFR 312.21

Phases of an Investigation

Phase 1:

- Includes **initial introduction** of an investigational new drug into humans
- Closely monitored and may be conducted in **patients or normal volunteer subjects**
- Designed to determine the **metabolism** and **pharmacologic actions** of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on **effectiveness**
- Generally **20-80 subjects**

Investigational New Drug Application
21 CFR 312.21
(cont'd)

Phase 2:

- Includes controlled clinical studies conducted to evaluate the **effectiveness** of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term **side effects and risks** associated with the drug
- Closely monitored
- Typically **no more than several hundred subjects**

Investigational New Drug Application
21 CFR 312.21
(cont'd)

Phase 3:

- Expanded controlled and uncontrolled trials
- Performed after preliminary evidence suggests effectiveness of the drug and intended to **gather additional info about effectiveness and safety**
- Typically **several hundred to several thousand subjects**

Investigational New Drug Application
ICH E8 3.1.3.4

Phase 4:

- All studies performed **after drug approval** and **related to the approved indication**

- May be **drug-drug interaction**, **dose response**, or **safety studies** and studies designed to **support use under the approved indication**

Investigational New Drug Application
21 CFR 312.30

Protocol Amendments

Covers the regulations related to:

- New protocols to an IND

- Changes in currently approved protocols - Amendments

Investigational New Drug Application
21 CFR 312.32

Serious Adverse Drug Experience: Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical event ***(ICH Guidelines)***

Investigational New Drug Application 21 CFR 312.52

Transfer of Obligations to a CRO

- A sponsor may transfer responsibilities for any or all of the obligations to a CRO. Such transfer shall be documented in writing. Any obligation not covered by the written description shall be deemed not to have been transferred.
- A CRO that assumes any obligation of a Sponsor shall be subject to the same regulatory action as a Sponsor for failure to comply with any obligation assumed under the regulations.

Investigational New Drug Application 21 CFR 312.53

Selecting Investigators and Monitors

Investigator Selection

- A Sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug
- Before permitting an investigator to begin participation in an investigation, the Sponsor shall obtain the following:
  - Form FDA-1572
  - Curriculum Vitae of investigator(s) to show the education, training, and experience of the investigator
  - Clinical Protocol
  - Financial Disclosure Information

Investigational New Drug Application 21 CFR 312.53 (cont'd)

Monitor Selection

- A Sponsor shall select a monitor qualified by training and experience to monitor the progress of the investigation

Investigational New Drug Application 21 CFR 312.56

Review of Ongoing Investigations

- A sponsor who finds that an investigator is noncompliant with the Form FDA 1572 shall promptly either secure compliance or discontinue the investigator's participation and shall notify the FDA

Investigational New Drug Application
21 CFR 312.60, 312.61, 31.62, 312.64, 312.66

General Responsibilities of Investigators

- Responsible for protecting the rights, safety, and welfare of subjects under his/her care
- Obtain informed consent for each subject screened
- Administer the test article only to subjects under the investigator's (or subinvestigator's) personal supervision

Investigational New Drug Application 21 CFR 312.60, 312.61, 31.62, 312.64, 312.66 (cont'd)

- Maintain adequate records for disposition of study drug
- Prepare and maintain adequate and accurate case histories (includes all CRFs, source documents, signed consent forms, progress notes, hospital chart, nurse's notes, etc.). The case history for each subject shall document that informed consent was obtained prior to participation in the study.
- Maintain study records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

Investigational New Drug Application 21 CFR 312.60, 312.61, 31.62, 312.64, 312.66 (cont'd)

- Promptly report to the Sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug
- Provide the Sponsor with an adequate report shortly after participation completion
- Provide Financial Disclosure reports to the Sponsor
- Promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others

Applications for FDA Approval to Market a New Drug
21 CFR Part 314

Applications for FDA Approval to Market a New Drug
21 CFR Part 314

This regulation covers the procedures and requirements for the submission to, and the review by, the FDA of applications to market a new drug as well as post-marketing reports to them

Protection of Human Subjects
21 CFR Part 50

Protection of Human Subjects 21 CFR 50

- Informed consent is a process beginning with the first contact to discuss the subject's interest in study participation and ending when the subject completes the study

Protection of Human Subjects 21 CFR 50.20

General requirements of the Informed Consent Document

- Must be written in a language understandable to the subject

- May not include any exculpatory language through which the subject or the LAR is made to waive any of the subject's legal rights, or releases or appears to release the investigator, the Sponsor, the institution, or its agents from liability for negligence

Protection of Human Subjects
21 CFR 50.20
(cont'd)

- The prospective subject or LAR must have sufficient opportunity to consider whether or not to participate

- There shall be no undue influence or possibility of coercion to participate

Protection of Human Subjects

Documentation of Informed Consent

- By the use of a written consent form approved by the IRB and signed/dated by the subject or the subject's LAR (21 CFR 50.27)
- The case history for each individual shall document that informed consent was obtained prior to participation in the study (21 CFR 312.62)
- A copy shall be provided to the person signing the form (21 CFR 50.27)

Protection of Human Subjects
21 CFR 50.25

Elements of Informed Consent

- Basic Elements of Informed Consent
- Additional Elements of Informed Consent

Protection of Human Subjects
21 CFR 50.25
(cont'd)

Basic Elements

- Statement that the study involves research, purpose of the research, duration of participation, description of procedures, identification of any experimental procedures

- Description of reasonably foreseeable risks or discomforts to the subject

- Description of any benefits to the subject or others that can reasonably be expected

Protection of Human Subjects
21 CFR 50.25
(cont'd)

- Disclosure of appropriate alternative procedures or treatment
- Description of the extent to which the confidentiality of records will be maintained, including a statement that the FDA may inspect the records
- Explanation of compensation and available medical treatments, if any, in case injury occurs; where to get additional information

Protection of Human Subjects
21 CFR 50.25
(cont'd)

- Explanation of whom to contact with questions about the research and research subject's rights and whom to contact in the event of a research-related injury

- Statement that participation is voluntary and that refusal to participate or discontinuation of participation at any time involves no penalty or loss of benefits to which the subject is otherwise entitled

Protection of Human Subjects
21 CFR 50.25
(cont'd)

Additional Elements

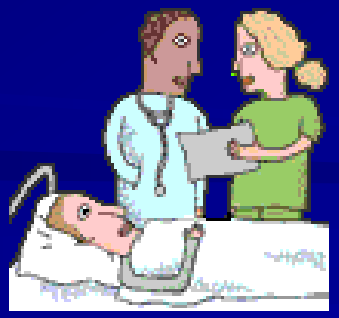
- Statement that the particular treatment or procedure may involve risks to the subject (or embryo or fetus if the subject is or becomes pregnant) which are currently unforeseeable

- Circumstances under which the subject's participation may be terminated without regard to the subject's consent

Protection of Human Subjects
21 CFR 50.25
(cont'd)

- Any additional costs associated with study participation

- Consequences of the subject's decision to withdraw and procedures for orderly termination of the subject's participation



Protection of Human Subjects
21 CFR 50.25
(cont'd)

- Significant new findings related to willingness to continue will be provided to the subject

- Approximate number of subjects involved in the study

Protection of Human Subjects
21 CFR 50.25
(cont'd)

Consent requirements

- Do not preempt any applicable federal, state, or local laws which require additional information be included in the consent form

- Do not limit the authority of a physician to provide emergency medical care as permitted by federal, state, or local law

21 CFR Part 50
Federal Register/ Vol 76. N 2/ 04 Jan 2011

- Inclusion of the following statement or similar facsimile: “A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.”

Protection of Human Subjects
ICH GCP 4.8.8 and 4.8.10

Other specific GCP consent requirements

- Trial treatments must be identified, along with the probability of random assignment to each treatment
- The subject's responsibilities
- Access to records by monitors, auditors, IRB/IEC, regulatory authorities
- Required signatures include the subject (or LAR) and the person conducting the informed consent discussion
- The subject (or LAR) should personally sign/date the consent form

Protection of Human Subjects
21 CFR 50.55

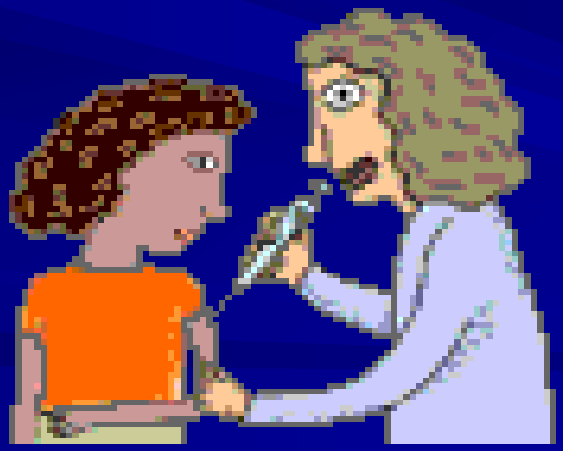
Requirements for Permission by Parents or Guardians and for Assent by Children

- The IRB must determine that adequate provisions are made for soliciting the assent of children when in the judgment of the IRB the children are capable of providing assent
- Takes into account the age, maturity, and psychological state of the children involved
- This judgment may be made for all children involved or for each child, as the IRB deems appropriate

Protection of Human Subjects
21 CFR 50.55
(cont'd)

- Age requirements for assent vary by state

- The IRB may waive the assent requirement, if appropriate



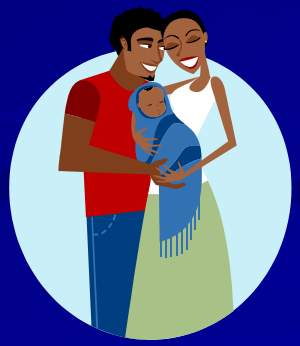
Financial Disclosure by Clinical Investigators
21 CFR Part 54

Financial Disclosure
21 CFR 54.4

The applicant is required to submit for each clinical investigator who participates in a study either a certification that no financial arrangements exist or disclose the nature of those arrangements to the FDA

Financial Disclosure
21 CFR 54.2

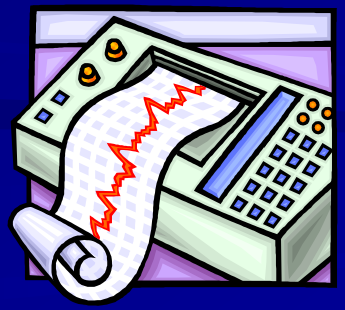
- Clinical Investigator: An Investigator or Sub Investigator who is directly involved in the treatment or evaluation of research subjects (All listed on Form FDA 1572)
- Also includes spouses and each dependent child of the investigator



Financial Disclosure
21 CFR 54.2
(cont'd)

Disclosure requirements:

- ***Excess of $25,000:***
  - Significant payments to investigator or institution by the Sponsor, exclusive of cost of conducting the study
  - Includes grants to fund ongoing research, equipment, or retainers for consultation or honoraria



Financial Disclosure
21 CFR 54.2
(cont'd)

Disclosure requirements:

- ***Excess of $50,000:***
  - Holdings in a publicly-traded company
  - Includes value of stock, ownership interest, and other financial interests

Financial Disclosure
21 CFR 54.4

Investigator Responsibilities

- Provide complete and accurate financial disclosure to the Sponsor. Sponsor will forward this to the FDA.

- Prompt update if relevant changes occur during the study or within one year following completion of the study.

Financial Disclosure
21 CFR 54

When in doubt, seek guidance from the FDA

Institutional Review Boards
21 CFR Part 56

Institutional Review Boards
21 CFR 56

Definition: Any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects

Primary Purpose: To assure the protection of the rights and welfare of the human subjects

Institutional Review Boards
21 CFR 56.104

Exemptions from IRB Requirement

This topic is covered in CFR but at this time is not applicable to Paragon studies.

Institutional Review Boards
21 CFR 56.107

IRB Membership

- At least 5 members; may not be all of the same gender
- Varying backgrounds; may not be all of the same profession

Institutional Review Boards
21 CFR 56.107
(cont'd)

- At least 1 member whose primary concern is in the scientific area and at least 1 member whose primary concerns are in non-scientific areas (e.g., lawyer, ethicist, clergy member)
- Diversity of racial and cultural background
- Sensitivity to attitudes and concerns of the community
- Knowledge of applicable regulations, laws, and standards of professional conduct and practice

Institutional Review Boards
21 CFR 56.107
(cont'd)

- At least 1 member not-affiliated with the institution (may be same individual as non-scientific member)
- No participation that represents a conflict of interest
- External experts may be invited to provide expertise not available on the IRB – may not vote with the IRB

Institutional Review Boards
21 CFR 56.108

IRB Function

- Follow written procedures
- Review and approve initiation of biomedical research involving human subjects
- Conduct continuing review – annually or more frequently
- Ensure prompt reporting to the IRB of changes in research activity
- Responsible for reporting serious or continuing noncompliance to institutional officials and the FDA

Institutional Review Boards
21 CFR 56.109

IRB Review of Research

- Have authority to:
  - Approve research activities
  - Require modifications in research activities
  - Disapprove research proposals
- Shall notify investigators in writing of its decisions to approve or disapprove the proposed research activity
- Establish review intervals depending on the degree of risk, but not less than once per year, and shall have the authority to observe, or have a third party observe, the consent process and the research

Institutional Review Boards
21 CFR 56.110

Expedited Review Procedures

- May be used for research involving no more than minimal risk and for minor changes in approved research
- IRB required to have a method of keeping all members advised of expedited approvals
- FDA may restrict, suspend, or terminate an IRB's use of expedited review procedures if necessary to protect the rights or welfare of subjects

Institutional Review Boards
21 CFR 56.111

Criteria for IRB Approval of Research

In order to approve a research proposal, the IRB shall determine that all of the following requirements are satisfied:

- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefits
- Selection of subjects is equitable (dependent on purposes of the research)
- Assured that informed consent will be sought from each prospective subject or LAR

Institutional Review Boards
21 CFR 56.111
(cont'd)

- Informed consent will be properly documented
- Assures monitoring of collected data, where appropriate, to ensure safety of subjects
- Adequate provisions to protect the privacy of study participants and confidentiality of their data
- Additional safeguards for vulnerable populations

Institutional Review Boards
21 CFR 56.113

Suspension or Termination of IRB Approved Research

- An IRB has the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects
- This suspension or termination must be reported promptly to the investigator, institutional officials, and the FDA

Institutional Review Boards
ICH GCP 3.1.2

The IRB/IEC should obtain:

- Protocol and amendments
- Written informed consent forms
- Subject recruitment procedures (ex: advertisements)
- Written information provided to subjects
- Investigator's Brochure

Institutional Review Boards
ICH GCP 3.1.2
(cont'd)

- Available safety information
- Information on payments and compensation available to subjects
- Current CV of investigator and/or other documentation of qualification
- Any other documents/information required by the IRB

Institutional Review Boards
21 CFR 56.115

IRB Records

The IRB shall prepare and maintain documentation of IRB activities:

- Copies of all research proposals, scientific evaluations, approved sample consent documents, investigator submitted progress reports, and reports of injuries to subjects
- Minutes of IRB meetings
- Records of continuing review activities

Institutional Review Boards
21 CFR 56.115
(cont'd)

- Correspondence between the IRB and Investigators
- List of IRB members
- Written IRB procedures
- Statements of significant new findings provided to subjects

Records shall be retained for at least 3 years after completion of the research