Clinical Trial Process for Drugs and Biologics: FDA Authority

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Clinical Studies

- Four phases of clinical investigation
- Phase I, II, and III investigations
  - To develop data on new products or new uses
- Phase IV investigations
  - To develop data on approved products and uses

Phase 1 Studies

- Initial Administration to human beings
- Small number of healthy subjects
- Assess toxicity, absorption, distribution, metabolism, elimination
- Focus
  - Safe dosage range
  - Appropriate route of administration

Phase 2 Studies

- Expanded Investigations
- Limited number of patients with targeted condition
- Focus
  - Effectiveness
  - Side effects and risks
  - Dosing

Phase 3 Studies

- Pivotal Efficacy Trials
- Large numbers of patients
- Reasonable assurance of safety and effectiveness from Phase 1 and 2 studies
  - End-of-Phase-II Meeting
- Focus
  - Primarily efficacy
  - Safety
  - Optimal dosing

Phase 4 Studies

- Post-approval studies
- May be required as a condition of approval
  - FDCA § 505(o)(3)
  - Accelerated approval regulations (21 CFR 310.303
- Focus generally on safety

IND Requirement

Notice of claimed investigational new drug exemption

- Required to conduct clinical research on drug subject to § 505
  - Unapproved product or unapproved use of approved product
- Exceptions
  - Use of product in the practice of medicine
  - Certain investigations for products lawfully marketed in the U.S.
    - Not intended to support significant changes in labeling or prescription drug advertising or to promote an investigational drug and
    - Not involving significant increased risk (or decreases acceptability of risk) associated with marketed drug
    - Institutional review board and informed consent are required
  - Bioequivalence studies not involving new chemical entities
  - Certain biologics intended for *in vitro* diagnostic use

IND Contents

- Chemical composition
- Preclinical data
- Training and expertise of investigators
- Protocol
- Informed consent
- Institutional Review Board (IRB)

IND Regulatory Process

- FDA review of IND to determine whether preclinical and other data show an unacceptable safety risk
- IND becomes effective after 30 days in absence of FDA hold
- Clinical holds
- Revocation
- IND records and reports
  - Protocol amendments
  - Safety reports
  - Annual reports

Good Clinical Practice Regulations

- 21 CFR 312
  - INDs
  - Foreign Clinical Trials Not Conducted under INDs
- 21 CFR 50
  - Protection of Human Subjects
  - Informed Consent
- 21 CFR 54
  - Financial Disclosure of Clinical Investigators
- 21 CFR 56
  - Institutional Review Boards
- 21 CFR 11
  - Electronic Records and Signatures
- Detailed list of regulations and guidance documents at:
  - http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm#FDARegulations

ICH Good Clinical Practice Guidance

- International Conference on Harmonization E6 Guidance: Good Clinical Practices
  - Uniform standards among the EU, Japan, and the US
  - Intended to facilitate acceptance of clinical data by regulatory authorities
- FDA adopted as FDA guidance document

Informed Consent

- Informed Consent
  - Ensure participation is voluntary
  - Disclosure of risks, potential benefits, and alternative courses of treatment
  - Right to withdraw consent at any time
- Signed informed consent document (ICD)
- Process that continues throughout study

Informed Consent

- Each subject must provide legally effective informed consent prior to participation in the study (21 CFR 50.25)
- Exceptions
  - Emergency Research
    - Research in emergency situations
    - IRB approval
  - Minor subjects
    - Parental permission
    - Child assent (as developmentally appropriate)

Informed Consent

- Process of informed consent
  - Must not be coercive
  - ICD wording understandable to the subject
  - Opportunity to have any questions answered prior to consenting
  - Opportunity to discuss study with others before consenting
  - Copy of signed and dated ICD
- HIPAA authorization
  - Disclosure of protected health information to sponsor, IRB, FDA, and others
  - In ICD or separate HIPAA authorization

IND: Required Participants

- Sponsor
  - Individual or entity that submits and is responsible for the IND
- Investigator
  - Individual who conducts the investigation
  - Responsible for team involved in research
- IRB
  - Independent professional review board
  - Approve and monitor study to protect human subjects

IND: Other Possible Participants

- Contract research organization (CRO)
  - Entity that assumes under contract with Sponsor certain regulatory obligations
- Monitor
  - Individual or entity designated by Sponsor to oversee progress of investigation
- Site Management Organization (SMO)
  - Entity that manages site
  - May hire investigator and staff

Sponsor Responsibilities

- File and maintain IND
- Select qualified investigators
- Keep appropriate records
- Provide necessary information to investigators to conduct the trial
  - Investigator's Brochure
- Monitor and oversee trial
- Review and evaluate data
- Submit records and reports to FDA

Sponsor Monitoring and Oversight

- Ensure compliance with protocol and regulations
- In case of noncompliant investigator, sponsor must:
  - Promptly secure compliance or:
    - Cease shipment of investigational drug to the investigator
    - Discontinue investigator's participation
    - Require destruction or return of all study drug in the investigator's possession
  - Inform FDA of its action

Sponsor Safety Reporting

Obligation to report to FDA and Investigators:

- Within 7 days of receipt of information
  - Unexpected fatal or life threatening experience associated with the use of study drug
- Within 15 days of receipt of information
  - Serious and unexpected adverse experience associated with the use of the study drug
  - Findings from other clinical, nonclinical, or *in vitro* testing that suggest a significant risk in humans exposed to the drug
  - Clinically important increase in rate of serious suspected adverse reactions listed in protocol or Investigators Brochure

Investigator Responsibilities

- Conduct study per protocol and regulations
- Maintain and retain records
- Control drugs under investigation
  - Administer only to enrolled subjects under investigator's supervision
  - Maintain records of investigational drug disposition
- Protect rights, safety, and welfare of subjects
  - Obtain informed consent
  - Ensure IRB oversight
- Submit records and reports to Sponsor

Investigator Safety Reporting

- Reporting to Sponsor
  - Immediately report any serious adverse event
    - Whether or not considered drug related
  - Include assessment of whether there is a reasonable possibility that the study drug caused the event
- Reporting to IRB
  - Promptly report:
    - Changes in research activity
    - Unanticipated problems involving risks to human subjects or others

IRB Institutional Obligations

- Registration with HHS
- Membership consistent with regulations
- Ensure and document compliance with policies consistent with regulations

IRB Oversight

- Review and approve clinical trial
  - Protocol
  - Investigators
  - ICD and informed consent process
  - Advertising materials
- Ensure risks are minimized and reasonable in light of anticipated benefits
- Approve changes in research
  - Except where necessary to eliminate apparent immediate hazards to human subjects
- Continuing review (at least annually)

Expanded Access INDs

- Serious and Life-Threatening Conditions
- No satisfactory alternative
- Treatment IND
  - Expanded access to broad spectrum of patients where there is regular IND for a promising therapy
- Individual Patient IND (including emergency IND)
  - Access for individual patient who cannot get into a study
  - Physician can apply
- Intermediate-Size Population IND
  - Consolidation of emergency INDs

Promotion of Investigational Drug

- FDA regulations prohibit promotion of safety and effectiveness of investigational drug
- Considered pre-approval promotion
- Scientific exchange permitted
  - Policies similar to promotion of off-label use

Foreign Studies Not Conducted under an IND

- Most foreign studies conducted under INDs
- Exception in 21 CFR 312.120
  - Compliance with Good Clinical Practices set forth in ICH E6
  - Review and approval by independent ethics committee (similar to IRB)
  - Documentation of informed consent
  - FDA can validate data through on-site inspection

END

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