Clinical Research Overview

Definitions and Introduction to Clinical Research

Clinical Research Center
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Clinical Research - Definitions

Research
“A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”

Clinical Research
Research that either directly involves a particular person or group of people or uses materials from humans, such as their behavior or samples of their tissue, that can be linked to a particular living person.
Clinical Research - Definitions

Human subject (45 CFR 46.102)

“A living individual about whom an investigator conducting research obtains
(1) data through intervention or interaction with the individual, or
(2) identifiable private information.”
Clinical Research - Definitions

The NIH definition of clinical research is:

**Patient-Oriented Research:**
This type of research involves a particular person or group of people or uses materials from humans. This research can include:
- Studies of mechanisms of human disease
- Studies of therapies or interventions for disease
- *Clinical trials*
- Studies to develop new technology related to disease
Clinical Research - Tips to Remember

➢ To answer questions about different diseases from information gathered from human subjects

➢ May involve patients’ records, or information that people give during health and lifestyle surveys

➢ A key branch is clinical trials testing new treatments/devices/drugs for safety and effectiveness
Pre-Clinical Research - Definition

The evaluation of a drug's toxic and pharmacologic effects through in vitro and in vivo laboratory animal testing

As per FDA requirement, the sponsor should:
(a) Develop a pharmacological profile of the drug
(b) Determine the acute toxicity of the drug in at least two species of animals, and
(c) Conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical studies
Pre-Clinical Research - Importance

- If the compound is found to be potentially unsafe or unlikely to work, no further tests will be done and it will not be developed further.

- For compounds with real potential to become medicines, pre-clinical research results decide the starter range of doses to be tested in people, as well as the format to be used (syrup, capsule, pill, injection, etc...).
Pre-Clinical Research - Importance

Under FDA requirements, a sponsor must first submit data showing that the drug is reasonably safe for use in initial, small-scale clinical studies.
References


http://www.mhra.gov.uk/Howweregulate/Medicines/Mymedicine/Pre-clinicalresearch/index.htm
Clinical Trials

- Aim to show the benefits and risks of new drugs or treatments, usually by comparing them to placebo or standard treatments in use

- Treatments given to patients or healthy members of the public

- Differences in their effects on the trial participants over time are observed and recorded

- The best way to assess the safety and efficacy of new treatments, their side effects, and their superiority over placebo or existing standard treatments
Clinical Trials - Definitions

Randomization

Process by which two or more alternative treatments are assigned to volunteers by chance rather than by choice

Single- or double-blind studies

- In single-blind studies, participants do not know which medicine is being used, so they can describe what happens without bias
- In a double-blind studies, neither participants nor members of the research team are told which patients are getting which medication, so that their observations will not be biased, in order not to influence the results
Clinical Trials - Definitions

Case Report Form (CRF)
A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject

Source document
Original documents, data, and records: e.g., hospital records, clinical and office charts, laboratory notes, subjects' diaries or evaluation checklists, recorded data from automated instruments, x-rays, subject files, etc...
References

http://www.hhs.gov/ohrp/humansubjects/guidance/invitrodev.html

http://www.nichd.nih.gov/health/clinicalresearch/

http://www.ct-toolkit.ac.uk/_db/_documents/MRC_clinical_research_leaflet.pdf

Clinical Trials - Phases

Clinical testing proceeds progressively in four phases (called Phases I, II, III, and IV), each phase more extensive than its predecessor.
Clinical Trials - Phase I Studies

- Initial introduction of an investigational new drug into humans
- Closely monitored and usually conducted in healthy volunteer subjects
- The total number of subjects is generally less than 100 persons
Clinical Trials - Phase I Studies

• Designed to determine:
  - The metabolic and pharmacologic actions of the drug in humans
  - The side effects associated with increasing doses, and,
  - If possible, to gain early evidence on effectiveness

• To evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans

• Basis of the design of well-controlled, scientifically valid, Phase II studies depending on pharmacokinetics and pharmacological findings
Clinical Trials - Phase II Studies

- To obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in subjects with the disease or condition
- To determine the optimal dose of the investigational product
- Helps determine the common short-term side effects and risks associated with the drug
- Well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred participants
Clinical Trials - Phase III Studies

- Additional information about effectiveness and safety to evaluate the overall benefit-risk relationship of the drug, after obtaining preliminary information through Phase II studies.

- Provide an adequate basis for extrapolating the results to the general population.

- Usually include several hundred to several thousand participants.
Clinical Trials - Phase IV Studies

- After a medicine has been licensed, put on the market and prescribed to patients

- It is part of the monitoring process; Designed to find out more about the long term harms and benefits of a medicine, and to discover new uses for it
Clinical Trials - Overview of FDA Approval Process

- Pre-clinical testing on animals (3 years)
- Investigational New Drug (IND) application outlines human clinical trials
- Phase I studies on less than 100 healthy people (1 year)
- Phase II studies on hundreds of participants (2 years)
- Phase III studies on hundreds to thousands of participants (3 years)
References


Roles and Responsibilities - Investigator

*Person responsible for the conduct of the clinical trial at a trial site. The responsible leader of the study team.*

- Qualified by education, training, and experience to assume responsibility for the proper conduct of the trial and the ethical performance of the project

- Has a thorough understanding of the protocol, and is familiar with the appropriate use of the investigational product(s), as described in the protocol

- Aware of, and complies with, GCP and the applicable regulatory requirements, institutional, local, and federal regulations
Roles and Responsibilities - Investigator

- Respond to subject’s complaints and/or request for more information

- Protects the rights, safety, and welfare of subjects under the investigator’s care

- Controls drugs, biological products, and devices under investigation (21 CFR 312.60, 21 CFR 812.100)

- Must submit a signed and dated Form FDA 1572 (Statement of Investigator) to the sponsor before participating in an FDA-regulated study to “ensure study conduct according to the investigational plan, and applicable regulation” for clinical investigations of drugs
Roles and Responsibilities - Investigator

- Ensures qualification and appropriate training of self and the research team, complete institutional certification and other requirements to conduct research involving humans (CITI and others)

- Seeks a written and dated approval from the IRB/IEC for the trial and all the trial-related documents before initiating it

- Reports to the IRB any changes to protocol during approval period and seeks approval for the changes before implementing them (except for emergencies)
Roles and Responsibilities - Investigator

- Reports unexpected results and SAE(s) to the IRB within 2-3 business days
- Reports to the IRB any problems/incidents, or protocol violations
- Complies with the IRB’s continuing review and approval requirements in a timely manner
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports
Roles and Responsibilities - Investigator

- Explains the protocol to subject and family and seeks informed consent/assent

- Ensures that adequate medical care is provided to a subject for any adverse events related to the trial, including clinically significant laboratory values

- Completes and signs the subject’s “research enrollment form” and ensures its placement in subject’s medical record (mainly biomedical protocols)

- Makes a reasonable effort to ascertain the reason(s) of a subject’s withdrawal from the study, while fully respecting the subject's rights
American University of Beirut Medical Center

Research Enrollment Form

Patient Name: ________________

Patient Number: ________________

Date of Birth: ____________

This patient is enrolled in the below mentioned study/clinical trial. Please contact the Primary Investigator (PI) before giving any treatment.

Protocol Number: 

Study Title: ____________________________

____________________________________

Study Period: ________________

PI Name: ____________________________

Informed Consent Signed:
  □ Yes
  By: □ Patient
      □ Representative (specify): ____________
      Date: ________________

RA Name: ____________ Signature: ______________________________________

Contact person _________ Extension Number/ Pager: ________________

Date: ___/___/______ (MM/DD/YYYY)
Roles and Responsibilities - Study Coordinator

*Person assisting the Investigator in essential study procedures and overall conduct*

- Is thoroughly familiar with the protocol
- Carefully implements all aspects of the protocol
- Prepares and submits documents to the IRB
- Interacts with/Acts as a link between sponsor (CRO), IRB, office staff, other department personnel
- Tracks study payments
- Maintains regulatory files
- Documents all study communications, and study progress
Roles and Responsibilities - Study Coordinator

- Recruits subjects
- Documents subject study visits
- Resolves queries on study data
- Fill CRF-s in an adequate and complete way
- Transcribes source information to CRFs
- Coordinates, prepares for, and participates in monitoring visits, audits, and inspections
- Orders study supplies and drugs as needed
- Develops and coordinates advertising
Roles and Responsibilities - Study Coordinator

- Screens subjects for eligibility
- Discusses study and conducts consent process
- Schedules study visits
- Ensures all visits, tests and procedures are completed in required time intervals
- Interviews and evaluates subjects at appropriate intervals
- Coordinates study subject reimbursement
- Reviews laboratory and clinical information for signs of adverse events
Roles and Responsibilities - Study Coordinator

- Promptly reports AE(s) to the PI based on their nature and severity
- Identifies, documents, reports and follows up on adverse events
- Maintains drug accountability
- Dispenses investigational product per protocol and under PI supervision
- Obtains, prepares, and ships biological specimens in a timely manner
- Ensures compliance with biosafety packing for materials transfer
Roles and Responsibilities - Sponsor

Individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Responsible for

- Implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s)

- Ensuring written agreements with the investigator/institution and any other parties involved with the clinical trial
Roles and Responsibilities - CRO

Contract Research Organization

*The organization to which any or all of the sponsor's trial-related duties and functions may be transferred*

- Ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor

- Clinical Research Associate (CRA) is a person employed by a sponsor, or by a CRO acting on a sponsor’s behalf, who monitors the progress of investigator sites participating in a clinical study
Subject Recruitment

While recruiting research participants, the following issues should be taken into consideration:

- Inclusion exclusion criteria
- No undue coercion
- No promises of cure beyond what is outlined in the protocol
- No vulnerability or undue influence
Subject Recruitment

- No claims that the drug/device is safe or effective for the purposes under investigation
- No claims that the drug/device is known to be superior to others
- Terms such as “new treatment”, “new medication”, “new drug” not used
- No promises of “free medical treatment”

Ref:

The Protocol

The contents of a trial protocol:

- Protocol title, protocol identifying number, and date.
- Name and description of the investigational product(s)
- A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial
- Summary of the known and potential risks and benefits, if any, to human subjects
The Protocol

- Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s)

- A detailed description of the objectives and the purpose of the trial

- A detailed description of the trial design

- Any amendment(s) should also bear the amendment number(s) and date(s)
Investigator’s Brochure

• A compilation of the clinical and nonclinical data on the investigational product(s)

• Information to facilitate the understanding of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures
Site Initiation

- Performed by sponsor or CRO
- Confirm receipt of clinical supplies with each site
- Review protocol requirements
- Review sponsor policy on CRF completion and correction
Site Initiation

- Confirm presence of all required documents, including IRB approval and the IRB approved consent form(s)

- Ensure establishment of study files

- Establish monitoring visit frequency and communicate to site
Monitoring

• Performed by sponsor or CRO

• Site visits by the CRA as scheduled/required

• Review protocol compliance, especially inclusion/exclusion requirements

• Review CRF’s and compare to source documents

• Assure required corrections are made
Monitoring

- Review drug accounting, storage, dispensing
- Check for new adverse events
- Collect any outstanding data from previously reported adverse events
- Assure that safety update letters sent to site have been sent to the IRB
Monitoring

- Meet with investigator and study coordinator to review study status, answer questions, etc...

- Document visit on written report

- Confirm date of next visit with site

- Written report of visit findings to investigator
Monitoring - AUBMC Policy

“Clinical Trials External Monitoring Visits-Audits by Sponsors” - CRC015

✓ Letter from sponsor to PI 8 days before the visit:
  - Date of visit,
  - Arrival time
  - Expected duration of the visit
  - Name of the clinical trial monitor (CTM)
  - Records required in addition to study records
  - Specific data to be reviewed (consistent with protocol)

✓ Monitoring requiring info from AUBMC medical records should be carried out in the Department of Medical Records (MRD)
Monitoring - AUBMC Policy

✓ The Director of the MRD will be notified by the PI 3 days prior to the visit date
  - PI name
  - Sponsor name
  - Trial title
  - CTM name conducting the monitoring
  - Information required

✓ CTMs are NOT allowed unaccompanied access to the subject’s AUB-MC medical records

✓ Protect the identity of subjects and maintain the confidentiality of personally identifiable medical information
Study Termination

• Performed by sponsor or CRO

• All CRFs collected, corrected and in-house

• No outstanding data for serious adverse events, deaths, or pregnancies

• Drug collected, inventories and returned to sponsor

• Investigator files complete and investigator instructed regarding storage duration
Study Termination

- Drug reconciled from inventory and shipping invoices
- Investigator briefed on procedure if notified of FDA audit
- IRB notified of termination
- Study file complete and ready for audit
References


4- Kriger Research Center (KRC) Online training for Biopharmaceutical Professionals – Cananda

