

CLINICAL TRIALS 101



History



Perhaps the first ever clinical trial was James Lind's demonstration in 1753 that citrus fruits cured scurvy. He compared the effects of various different acidic substances ranging from vinegar to cider, on groups of sailors, and found that the group who were given oranges and lemons had largely recovered from scurvy after 6 days.

- **Before one can initiate testing in human beings, they must conduct extensive pre-clinical or laboratory research.**
- **Research usually involves years of experiments in animal and human cells.**
- **If this stage of testing is successful, the sponsor then provides this data to the FDA requesting approval to begin testing in humans. This is called an Investigational New Drug Application (IND)**
- **If approved by the FDA, testing in humans begins. This is done through a formally written and approved protocol.**

What is a Protocol?

- **A study plan on which all clinical trials are based.**
- **Carefully designed to protect the health of participants**
- **Describes what types of people may participate in the trial (inclusion and exclusion criteria)**
- **Gives detailed schedule of tests, procedures, medications, dosages, and length of the study.**
- **Principal Investigator is responsible for assuring that the protocol is strictly followed for each participant**

Who Sponsors Clinical Trials?

- **Physicians**
- **Medical Institutions**
- **Foundations**
- **Voluntary Groups**
- **Pharmaceutical Companies**
- **Federal Agencies (cooperative group research)**
 - **NIH**
 - **NCI (ACRIN is funded through the NCI as a cooperative group)**
 - **DOD**
 - **VA**



Types of Trials

The most commonly performed clinical trials evaluate new drugs, medical devices, biologics, or other interventions on patients in strictly scientifically controlled settings, and are required for regulatory authority approval of new therapies. NIH organizes trials into 5 different categories.

- **Treatment Trials-** test experimental treatments, new combinations of drugs, or new approaches to surgery or radiology/radiation therapy.
- **Prevention Trials-** look for better ways to prevent disease in people who have never had them or prevent them from returning.
- **Diagnostic Trials-** conducted to find better tests or procedures for diagnosing a particular disease or condition.
- **Screening Trials-** test the best way to detect certain diseases or health conditions.
- **Quality of Life-** explore ways to improve comfort and the quality of life for individuals with chronic illness

Trial Phases

- **Pre-clinical studies**
- **Phase 0**
- **Phase I**
- **Phase II**
- **Phase III**
- **Phase IV**



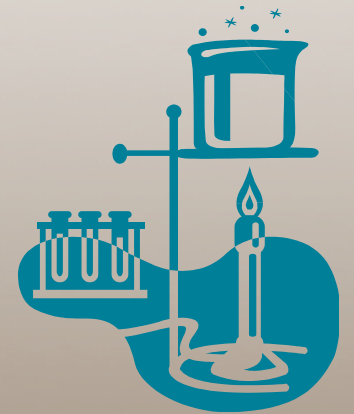


Pre-clinical Phase

- Involve *in vitro* (test tube or laboratory) studies and trials on animal populations.
- Wide ranging dosages of the compounds are introduced to the animal subjects or to an *in vitro* substrate.
- Obtain preliminary efficacy and pharmacokinetic information.
- Decisions are made during this phase regarding further development of the test compound, test item, or test article.

Phase 0

- **Recent designation for exploratory, first-in-human trials conducted in accordance with the FDA's 2006 Guidance on Exploratory Investigational New Drug (IND) Studies.**
- **Designed to expedite the development of promising therapeutic or imaging agents**
- **Involve the administration of single sub therapeutic doses to a small number of subjects (10-15).**
- **Gather preliminary data on the pharmacokinetic and pharmacodynamic properties and mechanism of action.**



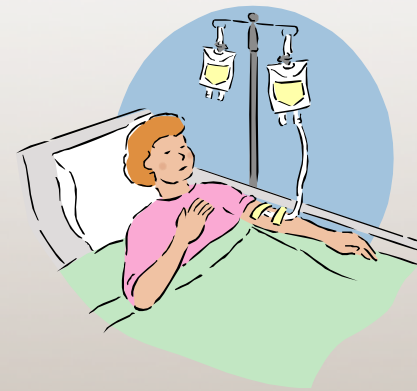
Phase I

- **First step in testing in humans.**
- **Researchers look for safety and potentially harmful side effects.**
- **Usually include only a limited number of human subjects (20-80).**
- **This phase of testing usually takes several months.**
- **Three different kinds of Phase I trials include:**
 - **SAD-single ascending dose studies**
 - **MAD-multiple ascending dose studies**
 - **Food Effect-investigates differences in absorption caused by eating pre-dose**



Phase II

- **Once a drug has shown to be safe, then it must be tested for efficacy.**
- **This phase may last from several months to two years.**
- **Usually involves several hundred patients**
- **Most of these trials are *randomized* trials**
- **Only about 1/3 of these studies successfully complete both phase I and phase II due to poor patient activity or toxic effects.**



Phase III

- **Randomized control trials on large patient groups (300-3000).**
- **Compare the results of the patients on the experimental trial to those patients utilizing standard diagnostic studies or treatment**
- **Studies move into this phase only after a diagnostic agent, modality, or treatments have shown promise in phase I and II trials.**
- **These trials are typically *multi-center* trials.**
- **Many phase III trials are *randomized* and *blinded*.**



Phase IV

- **Pre-approval, post-launch**
- **Involve safety surveillance and ongoing technical support of a drug.**
- **Sometimes mandated by the FDA for additional testing including interactions with other drugs and testing on certain populations.**
- **Adverse effects detected by Phase IV trials may result in withdrawal or restriction of a drug -recent examples include Vioxx.**





What is *Randomization*?

- **Researchers assign patients by chance to either a group taking the new diagnostic or treatment agent. Similar to “flipping a coin”.**
- **Randomization helps avoid bias.**
- **The assigned groups are often referred to as “arms”.**



Example: Patient #1 is assigned to Arm A of the trial, which involves the new modality or treatment. Patient #2 is assigned to Arm B, which is the standard modality or treatment.



What is a Blinded Study?

- In a single blinded study, the patient does not know which arm of the protocol they have been assigned to.
- This approach avoids bias because when people know what they are taking, it might change the way they react.



Example: Patients who know that they are assigned to the “new treatment” group might expect it to work better and report hopeful signs because they want to believe they are getting well. This could bias the study by making results look better than they are.

Blinded Trials *cont...*

- **Double blinded studies are those studies where neither the patient or the research physician know whether the patient is receiving the actual study drug or standard drug.**
- **When no standard is available, some studies compare new drugs with placebo drugs.**
- **All patients are informed of the possibility of being assigned to the placebo arm of a study**
- **Patients are “unblinded” only if it becomes medically necessary prior to the end of the study.**

**REGULATIONS
AND
RESEARCH APPROVAL**

Human Subject Protection Guidelines

- **Belmont Report**
 - Ethical Principals in Human Subjects Review
 - Respect, Beneficence, Justice
- **International Conference of Harmonisation (ICH)**
 - Brings together the regulatory authorities of Europe, Japan, and the US to discuss scientific aspects of human research.
- **Good Clinical Practices (GCP)**
 - Defines the roles and responsibilities of clinical trial sponsors, investigators, and monitors.
- **Declaration of Helsinki**
 - was developed by the World Medical Association (WMA), as a set of ethical principles for the medical community regarding human experimentation
- **Nuremberg Code**
 - set of principles for human experimentation set as a result of the Nuremberg Trials at the end of the second world war. Specifically, they were in response to the inhumane Nazi human experimentation carried out during the war by individuals such as Dr. Josef Mengele.

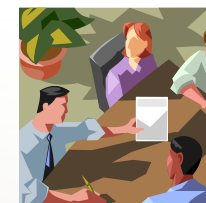
Institutional Review Board

- **A group of scientists, doctors, clergy, and consumers**
- **All clinical trials must be reviewed and approved by your local Institutional Review Board (IRB). The IRB reviews the protocol and patient consent to make sure the study is conducted fairly and participants are not likely to be harmed.**
- **The IRB also decides how often to review the trial once it has begun. They also decide whether the trial should continue as initially planned and what changes should be made.**
- **An IRB can stop a clinical trial if there are safety concerns, inappropriate trial oversight, or if evidence becomes available that a new intervention is effective, in order to make it widely available.**

Who is on the IRB?

FDA Requirements

- **Must have at least 5 members**
- **If studies include vulnerable populations, the IRB should have members who are familiar with these groups.**
- **Should include both men and women.**
- **Members should NOT be all of the same profession.**
- **Must include at least one scientist and one non-scientist**
- **Must include at least one person who is not affiliated with the institution, sometimes called “community members”.**
- **Members may not vote on their own projects.**
- **Only actual IRB members may vote (consultant may be used but can not vote).**





Informed Consent

- **The process in which a patient learns key facts about a research study and then voluntarily agrees to take part or decides against it.**
- **Informed consent must be documented by the use of a written consent form approved by the IRB for all ACRIN studies.**
- **Consent forms must be signed by the subject or the subject's legally authorized representative.**
- **A copy shall be given to the person signing the form.**

Consent Form Requirements

- **The consent form MUST include the following:**
 - **Statement that the study involves research**
 - **Explanation of the purposes**
 - **Expected duration of the subject's participation**
 - **Description of the procedures involved in the study**
 - **Identification of any procedures that are experimental**
 - **Risks or discomforts**
 - **Benefits**
 - **Alternatives to the research study**
 - **Statement of confidentiality**
 - **Statement about medical care and compensation should injury occur**
 - **Contact information for patients with concerns or questions**
 - **Statement that participation is voluntary and study withdrawal may take place at any time**

Who obtains written informed consent?

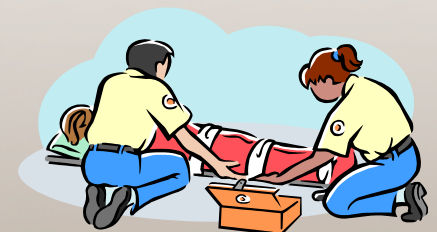
- **Principal Investigator**
- **Authorized Study Personnel** ✨
 - RA
 - RN
 - Research Coordinator / Designated Research Staff
- ❖ **An IRB may waive the requirement for the investigator to obtain a signed consent form if...**
 - The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context



ADVERSE EVENT REPORTING

What is an Adverse Event (AE)?

- **Any untoward medical occurrence in a patient who receives either an investigation agent or takes place in an investigational procedure or test.**
- **An adverse event does not always show relationship to the research investigation. It could be due to concurrent illness.**
- **Serious adverse events (SAE's) are those that include the following:**
 - **Events resulting in death**
 - **Life threatening events**
 - **Permanently disabling events**
 - **Events requiring hospitalization**
 - **Events resulting in persistent disability or incapacity**



Adverse Event Attribution

- **Unrelated-** the AE is *clearly not related* to research drug or exam
- **Unlikely-** the AE is *doubtfully related* to research drug or exam
- **Possible-** the AE *may be related* to the research drug or exam
- **Probable-** the AE is *likely related* to the research drug or exam
- **Definite-** the AE is *clearly related* to the research drug or exam

Adverse Event Reporting

- Only adverse events that are mandated in protocols and clinically relevant should be reported.
- Reporting and grading an AE simply reports that an event occurred
- The seriousness of the event should be reported
- The clinician must assign attribution of the event
- Follow ACRIN AE Reporting Procedures found on the ACRIN website at www.acrin.org

Adverse Events *cont....*

- **Adverse events can be:**
 - symptomatic**
 - asymptomatic**
 - clinically detected**
 - radiographically detected**
 - noted on lab studies or other testing**
- **An adverse event is a unique specific event used for medical documentation and scientific analysis**

CLINICAL TRIALS MANAGEMENT

“POTPOURRI”



MANAGING YOUR OFFICE AND TIME

- **Organization is key!**
- **Use your wastebasket frequently- research shows that we only use about 20% of what we keep!**
- **Manage your “to do” list effectively. This can be divided into two categories.**
 - Those that have to be done at a specific time
 - Those that are open-ended
- **Implement a system to keep track of names and telephone numbers, either electronically or on a paper rolodex.**
- **Create a filing system for your CRF’s that works easily and consistently.**
- **Remember, neat and organized are NOT the same thing!**
- **Manage your time in meetings. If you are coordinating the meeting, always use an agenda, and stick to it!**

TIPS FOR MANAGING YOUR CRF'S

- Set up patient folders ahead of study initiation. Include the most current version of the following:
 - Consent form
 - Eligibility checklist
 - Study initiation case report form
- Make sure to include ALL source documents with your CRF's.
- Color code your CRF/patient folders by study.
- Always use GCP when completing case report forms.
ex: ct colonography TP 9/21/07
~~barium enema~~
- Include a patient study calendar to keep track of study required activities in each patient CRF file.
- Complete the CRF as soon as you can. Get it submitted as soon as it is completed and mark it off as complete on the patient calendar.



- Utilization of the ACRIN Ops Tool to manage your calendars, forms due, reports due, etc....
- Extremely helpful when running more than one ACRIN trial or trials with numerous participants
- Preprinted forms can be produced
- Tracking of important IRB dates

IMPORTANT REMINDER

When faxing or mailing forms remember to remove all patient identifiers and use the provided labels or the following format for ACRIN

Form/Report Type:

Institution ID:

Study #:

Case #:

Make sure this information is provided on EACH page you are faxing or mailing!

- **Definition of Source Document/Data**

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

- **Original documents or certified copies can include the following:**

- Hospital records
- Clinic and office chart records
- Laboratory notes
- Patient diaries
- Pharmacy dispensing records
- Photographic negatives
- X-rays



COMMON AUDIT FINDINGS

- **Protocol non-compliance**
 - Inclusion/exclusion violations
 - Under-reporting of adverse events
 - Non-compliance with protocol required tests
 - GCP issues
- **Inadequate source documents**
 - Discrepancies between source and CRF
 - Poor documentation of attempted patient follow up
 - Lack of documentation in the source document that the patient was a research participant
- **Inadequate investigational product records**
 - Inconsistencies between the inv drug log and CRF
 - Lack of documentation of return of unused agents
- **Informed consent issues**
 - Research procedures done prior to consent signed
 - Failure of revised consents being used
 - Unapproved versions of consent being used

