An Introduction To Clinical Research

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How a bill becomes a law? How an experiment becomes a drug..

- 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 being 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

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
- Nuremburg 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.

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

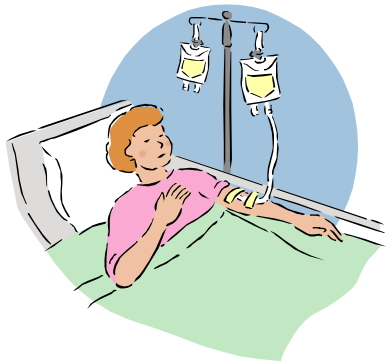
- Recent designation for exploratory, first-in-human trials conducted in accordance with the FDA's 2006 Guidance on Exploratory Investigational New Drug (IND) Studies.
- Designed to expedite the development of promising therapeutic or imaging agents
- Involve the administration of single sub therapeutic 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.

Overview of key entities and their roles

- Sponsor
- CRO
- Site
- Investigator

Key parts of a research practice site

- Study coordinator
- Regulatory administrator
- Quality Improvement (QI)
- PI
- Subject recruitment
- Facilities requirements:
  - Locked Pharmacy
  - Calibrated equipment
  - (clinical laboratory improvement amendment) CLIA waived lab
    - centrifuge/fridge/basic blood/urine processing
  - Physical space for storing source documents.

The clinical trial study: from study site selection to study closeout

- Pre-site selection survey
- Site selection visit
- CTA process ….

The clinical trial study: from study site selection to study closeout (cont'd)

- Site initiation visit
- Regulatory/IRB submission and approval
- Study in enrollment
- Follow up
- Monitoring visits
- Closeout

Closing Thoughts

- Is clinical research right for you?
- Benefits to your medical practice
  - Financial
  - Avenue for helping your patients get the latest in treatment
  - Enjoyable clinical experience
  - Opportunity to contribute to medical therapy.

Challenges to keep in mind

- High barrier to entry.
- Adopt a “clinical research physician” mindset.