



CLINICAL CENTER NURSING & PATIENT CARE SERVICES

Five Minute Forum

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Phases of Clinical Drug Trials

Prepared by: Holly Wieland, RN, MPH
Chair, Professional Development Committee

Background: A learning needs assessment was completed by the Clinical Center nursing staff in the Fall of 2002 which identified a need for better understanding of the different phases of Clinical Drug Trials.

Phase I Trials:

- Phase I studies include the initial introduction of an investigational new drug (IND) into humans.
- Phase I studies are **designed to determine safety, metabolism, and pharmacologic actions of the drug in humans**. Pharmacologic actions of interest may include bioavailability, volume of distribution, protein binding, clearance, and excretion.
- Phase I studies are **designed to learn about side effects associated with increasing doses**, i.e. dose limiting toxicities (DLT), maximum tolerated doses (MTD), and reversibility of side effects.
- Although Phase I studies may gain early evidence of effectiveness, they are not designed to measure effectiveness.
- Phase I studies are closely monitored and may be conducted in patients, or in normal volunteers.
- Phase I studies typically enroll 10-80 subjects but the numbers may vary. Subjects may be enrolled in cohorts of three or four at each dose level.
- Phase I studies expect to obtain sufficient information about pharmacokinetics and pharmacological effects to permit the design of well-controlled, scientifically valid Phase II studies.



Phase II Trials:

- Phase II studies are conducted **to evaluate the therapeutic effectiveness of the drug**, i.e. what types of diseases, tumors, conditions, etc. respond to the drug. Does the drug have the desired response?
- Phase II studies evaluate the common short term side effects and the risks associated with the drug to determine a risk/benefit profile.
- Phase II studies evaluate the dose response relationship. There must be measurable disease for the Phase II studies.
- Phase II studies are well-controlled clinical trials and are generally used when the standard treatment has not been effective.
- Phase II studies are closely monitored and are conducted in a relatively small number of patients, usually no more than several hundred.
- After Phase II studies show safety and effectiveness, the drug may move to a Phase III study.



Phase III:

- Phase III studies are performed after preliminary evidence suggesting effectiveness of the drug has been obtained.
- Phase III studies are usually randomized controlled trials where participants are randomly assigned to one or more groups. In a study with two groups, one group gets the standard treatment or placebo and is called the control group. The second group gets the new treatment being tested and is called the investigational group.
- Phase III studies evaluate efficacy as measured by disease response, survival, and quality of life factors, and **compare the new therapy with standard treatment**.
- Phase III studies may gather additional information about effectiveness and safety.
- Phase III studies evaluate the overall risk-benefit relationship of the drug and provide an adequate basis for product labeling.
- Phase III studies usually include several hundred to several thousand subjects.
- After the Phase III studies show safety and efficacy, the drug may be approved by the FDA and be marketed, and in some cases may move into a Phase IV study.



Phase IV:

- The primary objective of Phase IV studies is to **integrate new treatment into primary treatment**.
- Phase IV studies are conducted by request from the FDA to obtain additional information about the drug's risks, benefits, and optional use.
- Post marketing surveillance or observation by the FDA may be conducted with Phase IV studies.
- Phase IV studies are studies used on the general population and rely on physicians or other users to report adverse events.
- Phase IV studies could include studying different doses or schedules of administration than were used in the Phase II protocols, use of the drug in other patient populations, use of the drug at other stages of disease, or use of the drug over a longer period of time.

Frequently Asked Questions:

1. What is the primary objective of Phase I clinical trials?
2. What is the primary objective of Phase II clinical trials?
3. What is the primary objective of Phase III clinical trials?
4. What is the primary objective of Phase IV clinical trials?
5. In what phase/phases may unexpected side effects occur?

Answers:

1. Safety
2. Effectiveness
3. Efficacy, and to compare new therapy with standard therapy
4. To integrate new treatment into primary treatment
5. Phase I, Phase II, Phase III, Phase IV

References:

Protomechanics, Third Edition, 2000

NCI Fundamentals of Clinical Trials, January 2002

<http://cancer.gov/clinicaltrials/resources/basicworkbook>, March 2003.

Questions? Contact Holly Wieland [address:hwieland@mail.cc.nih.gov](mailto:hwieland@mail.cc.nih.gov)

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