CRC CERTIFICATION PREPARATION COURSE

SESSION 2B
PROTOCOL AND AMENDMENTS

Ruth A. Mulnard, DNSc, RN, FAAN

Professor Emeritus, Nursing Science

Associate Director, ICTS

Session 2B

- Clinical Trial Phases
  - Drug Trials
  - Device Trials
- Study Design
- Purpose and Objectives of Protocol
- Inclusion / exclusion criteria
- Study procedures
- Statistical plan
- Amendments to the protocol
  - Regulatory notifications
  - IND / IDE amendments

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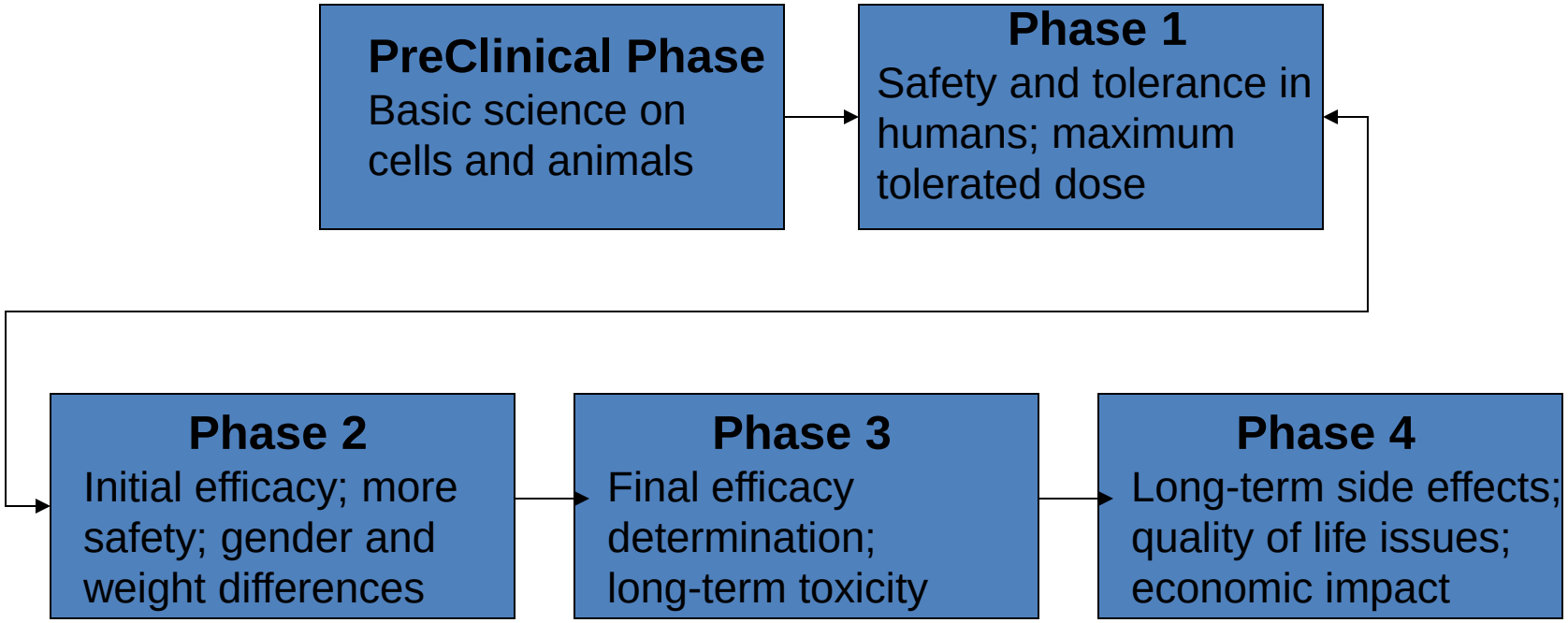
Clinical Trial Phases - Drugs



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Clinical Trial Phases - Drugs

- Phase I
  - First exposure in humans – small number exposed
  - Usually conducted on healthy individuals
  - Safety and tolerability are key goals
  - MTD
  - Bioavailability, PK studies

- Phase II
  - Conducted in disease-targeted individuals
  - Safety assessment remains key goal
  - Initial probe of efficacy
  - Number of participants - up to several hundred

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Clinical Trial Phases - Drugs

- Phase III
  - Final confirmatory trial before FDA approval
  - Larger sample size (several hundred to thousand)
  - Randomized, double-blind design very common
  - Safety and efficacy are key goals
  - Close monitoring of side effects
- Phase IV
  - Occurs after FDA approval
  - Evaluates general use in population with side effect

Clinical Trial Phases

- Medical Device Trials
  - Feasibility
  - Pivotal

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Study Design Parameters

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Clinical Trial Protocol Contents

- General Information
  - Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s)
  - Name and address of the sponsor and monitor (if other than the sponsor)
  - Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor
  - Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial
  - Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s)
  - Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator)
  - Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial

Clinical Trial Protocol Contents

- Background Information
  - 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
  - Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s)
  - Statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s)
  - Description of the population to be studied
  - References to literature and data that are relevant to the trial, and that provide background for the trial

Purpose / Objectives

- Trial Objectives and Purpose
  - A detailed description of the objectives and the purpose of the trial.

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Trial Design

- Trial Design – scientific integrity depends substantially on the trial design
  - Primary endpoints and the secondary endpoints
  - Description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.
  - Description of the measures taken to minimize/avoid bias, including:
    - (a) Randomization.
    - (b) Blinding.
  - A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s).

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Clinical Trial Design

- Trial Design
  - Expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any
  - Description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial
  - Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any
  - Maintenance of trial treatment randomization codes and procedures for breaking codes
  - The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data

Inclusion / Exclusion

- Subject Selection and Withdrawal
  - Inclusion criteria
  - Exclusion criteria
  - Withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
    - (a) When and how to withdraw subjects from the trial/ investigational product treatment
    - (b) The type and timing of the data to be collected for withdrawn subjects
    - (c) Whether and how subjects are to be replaced
    - (d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment

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Treatment and Procedures

- Treatment of Subjects
  - The treatment(s) to be administered
    - name(s) of all the product(s), dose(s), dosing schedule(s), route/mode(s) of administration, and treatment period(s), including the follow-up period(s) for subjects
  - Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial
  - Procedures for monitoring subject compliance
- Specific Study Procedures
  - Detailed by visit

Efficacy Assessments

- Assessment of Efficacy
  - Specification of the efficacy parameters
  - Methods and timing for assessing, recording, and analyzing of efficacy parameters

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Safety Assessment

- Assessment of Safety
  - Specification of safety parameters
  - The methods and timing for assessing, recording, and analyzing safety parameters
  - Procedures for eliciting reports of and for recording and reporting adverse event and concomitant illnesses
  - The type and duration of the follow-up of subjects after adverse events

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Statistical Plan

- Statistics
  - Statistical methods to be employed, including timing of any planned interim analysis (ses)
  - Number of subjects planned to be enrolled. In multi-center trials, the numbers of enrolled subjects projected for each trial site should be specified
  - Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification
  - The level of significance to be used

Statistical Plan

- Statistics
  - Criteria for the termination of the trial
  - Procedure for accounting for missing, unused, and spurious data
  - Procedures for reporting any deviation(s) from the original statistical plan (described and justified in protocol and/or in the final report, as appropriate)
  - The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects)

Source Documents – Data Review

- Direct Access to Source Data/Documents
  - The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s) / institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents

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Ethical Considerations

- Ethics
  - Description of ethical considerations relating to the trial

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Amendments to Protocol

- All amendments, no matter how minor, require submission to regulatory authorities:
  - IRB must review and approve before proceeding
    - Should submit ASAP – no delay
  - Radiation safety if changes in radiation exposure
  - Pharmacy review if drug handling / storage is amended
- Types of amendments:
  - Sponsor changes (e.g., alterations in procedures, monitoring of participants, safety-related changes)
  - Local changes – e.g., staff changes

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Amendments

- IND Amendments
  - FDA Form 1571

- IDE Amendments

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