Chapter 5: Additional Issues in Phase III Clinical Trials

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Double blinding

Double blinding: neither patient, physician nor evaluator are aware which treatment the patient is receiving.

- The patient— psychological benefit
- The treatment team— management and care of patients may be different
- The evaluator— try to make endpoint objective

Other methods to reduce bias:

- Make treatments to be compared look, taste, feel similar, etc.
- Use **placebo** when no best treatment is available

The Hippocratic Oath

I swear by Apollo the physician, by Aesculapius, Hygeia and Panacea, and I take to witness all the gods, all the goddesses, to keep according to my ability and my judgment the following Oath...

Modern version:

I swear to fulfill, to the best of my ability and judgment, this covenant: I will respect the hard-won scientific gains of those physicians in whose steps I walk, and gladly share such knowledge as is mine with those who are to follow...

IRB

IRB: Institutional Review Board or Internal Review Board

1. The risks to the study participants are minimized
2. The risks are reasonable in relation to the anticipated benefit
3. The selection of study patients is equitable
4. Informed consent is obtained and appropriately documented for each participant
5. There are adequate provisions for monitoring data collected to ensure the safety of the study participants
6. The privacy of the participants and confidentiality of the data are protected

The Protocol Document

Definition: a scientific document for a medical study on human subjects; contains background, experimental design, patient population, treatment and evaluation details, and data collection procedures.

Purposes

1. To assist investigators in thinking through the research
2. To ensure that both patient and study management are considered at the planning stage
3. To provide a sounding board for external comments
4. To orient the staff for preparation of forms and processing procedures
5. To provide a document which can be used by other investigators who wish to confirm (replicate) the results

The Protocol Document

A protocol generally has the following elements:

1. **Schema**: Depicts the essentials of a study design.
   WHI: page 18
2. **Objectives**: The objectives should be few in number and should be based on specific quantifiable endpoints
   WHI: pages 14-15 and pages 22-24
3. **Project background**: This section should give the referenced medical/historical background for therapy of these patients.
   WHI: pages 2-13
   This generally includes
   1. standard therapy
   2. predecessor studies (phase I and II if appropriate)
   3. previous or concurrent studies of a similar nature
   4. moral justification of the study

The Protocol Document

4. **Patient Selection**: A clear definition of the patient population to be studied. This should include clear, unambiguous inclusion and exclusion criteria that are verifiable at the time of patient entry. Each item listed should be verified on the study forms.
   WHI: pages 24-28
5. **Randomization/Registration Procedures** This section spells out the mechanics of entering a patient into the study
   WHI: pages 29-38
6. **Treatment Administration and Patient Management**: How the treatment is to be administered needs to be specified in detail. All practical eventualities should be taken into account, at least, as much as possible. Protocols should not be written with only the study participants in mind. Others may want to replicate this therapy such as community hospitals that were not able to participate in the original study.
   WHI: pages 18-22 and 44-49

The Protocol Document

7. **Study parameters**: This section gives the schedule of the required and optional investigations/tests.
   WHI: pages 38-39
8. **Statistical Considerations**:
   WHI: pages 52-55 and an extensive appendix
   - Study outline, stratification and randomization
   - Sample size criteria: Motivation for the sample size and duration of the trial needs to be given. This can be based on type I and type II error considerations in a hypothesis testing framework or perhaps based on the desired accuracy of a confidence interval.
   - Accrual estimates
   - Power calculations
   - Brief description of the data analysis that will be used
   - Interim monitoring plans

The Protocol Document

9. **Informed Consent** The consent form needs to be included.
    1. an explanation of the procedures to be followed and their purposes
    2. a description of the benefits that might reasonably be expected
    3. a description of the discomforts and risks that could reasonably be expected
    4. a disclosure of any appropriate alternative procedures that might be advantageous
    5. a statement that the subject is at liberty to abstain from participation in the study and is free to withdraw at any time
10. **Study Management Policy**: This section includes how the study will be organized and managed, when the data will be summarized and the details of manuscript development and publication
WHI: pages 58-61