5 Some Additional Issues in Phase III Clinical Trials

5.1 Blinding and Placebos

Even in a randomized trial the comparison of treatments may be distorted if the patients and those responsible for administering the treatment and evaluation know which treatment is being used. These problems can be avoided in some cases by making the trial double blind, whereby, neither patient, physician nor evaluator are aware which treatment the patient is receiving.

- The patient— If the patient knows he/she is receiving a new treatment then this may result in psychological benefit. The degree of psychological effect depends on the type of disease and the nature of treatments. One should not underestimate the importance of psychology for patients with disease. Whether it is asthma, cancer, heart disease, etc, the manner in which patients are informed of therapy has a profound effect on subsequent performance.

- The treatment team—(anyone who participates in the treatment or management of the patient). Patients known to be receiving a new therapy may be treated differently than those on standard treatment. Such difference in ancillary care may affect the response.

- The evaluator— It is especially important that the individual or individuals evaluating response be objective. A physician who has pre-conceived ideas how a new treatment might work may introduce bias in his/her evaluation of the patient response if they know the treatment that the patient received.

The biases above may be avoided with proper blinding. However, blinding treatments takes a great deal of care and planning. If the treatment is in the form of pills, then the pills for the different treatments should be indistinguishable; i.e the same size, color, taste, texture. If no treatment is to be used as the control group then we may consider using a placebo for patients randomized to the control group. A placebo is a pill or other form of treatment which is indistinguishable from the active treatment but contains no active substance. (sugar pill, saline, etc.) If you are comparing two active treatments each, say, with pills that cannot be made to be similar, then we may have to give each patient two pills; one active pill for one treatment
and a placebo pill for the other treatment. (This can become overwhelming if we are comparing different combinations of drugs).

It has been well documented that there is a placebo effect. That is, there have been randomized studies conducted that gave some patients placebo and the other patients nothing with the placebo group responding significantly better. Consequently, in a randomized clinical trial which compares a new drug to a placebo control, we are actually testing whether the active drug has effect equal to or greater than a placebo effect.

One must realize that although the principles of blinding are good, they are not feasible in some trials. For example, if we are comparing surgery versus chemotherapy in a cancer clinical trial, there is no way to blind these treatments. In such cases we must be as careful as possible to choose endpoints that are as objective as possible. For example, time to death from any cause.

5.2 Ethics

Clinical trials are ethical in the setting of uncertainty.
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:

To consider dear to me as my parents him who taught me this art; to live in common with him and if necessary to share my goods with him; to look upon his children as my own brothers, to teach them this art if they so desire without fee or written promise; to impart to my sons and the sons of the master who taught me and the disciples who have enrolled themselves and have agreed to the rules of the profession, but to these alone, the precepts and the instruction. I will prescribe regimen for the good of my patients according to my ability and my judgment and never do harm to anyone. To please no one will I prescribe a deadly drug, nor give advice which may cause his death. Nor will I give a woman a pessary to procure abortion. But I will preserve the purity of my life and my art. I will not cut for stone, even for patients in whom disease is manifest; I will leave this operation to be performed by practitioners (specialists in this art). In every house where I come I will enter only for the good of my patients, keeping myself far from all intentional ill-doing and all seduction, and especially from the pleasures of love with women or men, be they free or slaves. All that may come to my knowledge in the exercise of my profession or outside of my profession or in daily commerce with men, which ought not to be spread abroad, I will keep secret and I will never reveal. If I keep this oath faithfully, may I enjoy life and practice my art, respected by all men and in all times; but if I swerve from it or violate it, may the reverse be my lot.
Even today physicians may take the Hippocratic oath although it is not repeated in full. Clearly many of the issues, such as abortion, surgery for kidney stones, use of deadly drugs, no longer apply. Nor does the pledge for “free instruction” still apply.

Ethical considerations have been addressed by the Nuremberg Code and Helsinki Declaration (see xeroxed notes for more details)

In the United States, the Congress established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research as part of the National Research Act. This act required the establishment of an Institutional Review Board (IRB) for all research funded in whole or in part by the federal government. These were later modified to require IRB approval for all drugs or products regulated by the Food and Drug Administration (FDA).

IRB’s must have at least five members with expertise relevant to safeguarding the rights and welfare of patients participating in biomedical research. At least one should be a scientist, and at least one must not be affiliated with the institution. The IRB should be made up of individuals with diverse racial, gender and cultural backgrounds. The scope of the IRB includes, but is not limited to consent procedures and research design.

IRB’s approve human research studies that meet specific prerequisites.

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

5.3 The Protocol Document

Definition: The protocol is a scientific planning document for a medical study on human sub-
jects. It contains the study 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

I will hand out an example of a protocol from the Cancer and Leukemia Group B (CALGB) study 8541.

CALGB 8541 is a study of different regimen of adjuvant CAF (combination of Cyclophosphamide, Adriamycin and 5 Fluorouracil (5-FU)) as treatment for women with pathological stage II, node positive breast cancer. Specifically, intensive CAF for four cycles versus low dose CAF for four cycles versus standard dose CAF for six cycles will be compared in a three arm randomized clinical trial.

Protocols generally have the following elements:

1. **Schema.** Depicts the essentials of a study design.
   CALGB 8541: page 1

2. **Objectives** The objectives should be few in number and should be based on specific quantifiable endpoints
   CALGB 8541: page 3

3. **Project background** This section should give the referenced medical/historical background for therapy of these patients.
This generally includes

- standard therapy
- predecessor studies (phase I and II if appropriate)
- previous or concurrent studies of a similar nature
- moral justification of the study

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.

5. **Randomization/Registration Procedures** This section spells out the mechanics of entering a patient into the study.

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.

7. **Study parameters** This section gives the schedule of the required and optional investigations/tests.

8. **Statistical Considerations**

   - 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

9. **Informed Consent** The consent form needs to be included.

For CALGB 8541 this is in an appendix (not included)

The informed consent should include

- an explanation of the procedures to be followed and their purposes
- a description of the benefits that might reasonably be expected
- a description of the discomforts and risks that could reasonably be expected
- a disclosure of any appropriate alternative procedures that might be advantageous
- 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

CALGB 8541: Was not included