STUDY DESIGNS

IN BIOMEDICAL RESEARCH

INTRODUCTION TO CLINICAL TRIALS

SOME TERMINOLOGIES

- Research Designs: Methods for data collection
- Clinical Studies: Class of all scientific approaches to evaluate Disease Prevention, Diagnostics, and Treatments.
- Clinical Trials: Subset of clinical studies that evaluates Investigational Drugs; they are in prospective/longitudinal form (the basic nature of trials is prospective).

TYPICAL CLINICAL TRIAL

Study Initiation

Study Termination

No subjects enrolled after π_1

Enrollment Period, e.g. three (3) years

Follow-up Period, e.g. two (2) years

OPERATION: Patients come sequentially; each is enrolled & randomized to receive one of two or several treatments, and followed for varying amount of time- between π_1 & π_2

In clinical trials, investigators apply an “intervention” and observe the effect on outcomes. The major advantage is the ability to demonstrate causality; in particular: (1) random assigning subjects to intervention helps to reduce or eliminate the influence of confounders, and (2) blinding its administration helps to reduce or eliminate the effect of biases from ascertainment of the outcome.

Clinical Trials form a subset of cohort studies but not all cohort studies are clinical trials because not every research question is amenable to the clinical trial design. For example: (1) By ethical reasons, we cannot assign subjects to smoking in a trial in order to learn about its harmful effects, or (2) It is not feasible to study whether drug treatment of high LDL-cholesterol in children will prevent heart attacks many decades later.

In addition, clinical trials are generally expensive, time consuming, address narrow clinical questions, and sometimes expose participants to potential harm. For these reasons, clinical trials are best reserved for relatively “mature” research questions, and when observational studies strongly suggest that an intervention might be effective and safe. Even then, ones should learn to conduct these major studies in a responsible way to ensure success and to protect participants.

ETHICS OF CLINICAL TRIALS

- Clinical trials are mostly confirmatory; or so believed by investigators.
- According to the principle of "Good Medicine", physicians are obligated to work for better treatments for disease; then why putting a patient in a trial where that patient has 50% chance of receiving a treatment/placebo which is believed to be second best?
- We could argue that there are a number of other factors that counterbalance this ethical dilemma, that counterbalance any disadvantage to the patient and accrue to his/her net benefit.

Here is a short list of ethical supports for the modern physician-scientists:

(i) An informed consent is required;

(ii) Many patients cannot get the new treatment unless he/she participates in a clinical trial – in fact, results of both treatment often turn out substantially better than anticipated;

(iii) In many clinical trials, patients do get better for a number of reasons (closer, nursing attention, more frequent lab tests, more frequent visits and care by study physicians);

(iv) Placebo effects;

(v) Patients are often promised the new treatment later if it turns out more effective and he/she got assigned to placebo arm; and

(vi) The trial is terminated as evidence emerged that the new treatment is more superior

There are two commonly used study designs in clinical research. In a **parallel study design**, each subject is randomly assigned to one and only one of two or several treatments. A **crossover design study** is a longitudinal study in which each subject receives a sequence of different treatments, and there is a washout period between two treatments.

Crossover designs will be covered in the next lecture; we first introduce a few simple parallel study designs before talking steps in the design process.

The simplest form of designed experiments is the “completely randomized design” where treatments are randomly assigned to the experimental units – regardless of their characteristics. This design is most useful when the experimental units are relatively homogeneous with respect to known confounders.

A confounder is a factor which may be related to the treatment and the outcome even the factor itself may not be under investigation. A study may involve one or several confounders. In a clinical trial, the primary outcome could be SBP reduction and the baseline SBP is a potential confounder. Patients' age may be another one. In theory, values of confounders may have been balanced out between study groups because patients were randomized. But it is not guaranteed; especially if the sample size is not very large.

If confounder or confounders are known, heterogeneous experimental units are divided into homogeneous “block”; and randomizations of treatments are carried out within each block. The result would be a “randomized complete block design”.

A Simple Example:

An experiment on the effect of Vitamin C on the prevention of colds could be simply conducted as follows. A number of n children (the sample size) are randomized; half were each give a 1,000-mg tablet of Vitamin C daily during the test period and form the “experimental group”. The remaining half , who made up the “control group” received “placebo” – an identical tablet containing no Vitamin C – also on a daily basis. At the end, the “Number of colds per child” could be chosen as the outcome/response variable, and the means of the two groups are compared.

Some other factors might affect the numbers of colds contracted by a child: age, gender, etc… Let say we focus on gender.

THE CHOICES

- We could perform complete randomization – disregard the gender of the child, and put Gender into the analysis as a covariate (in a regression model); or
- We could randomize boys and girls separately; at the end the proportions of boys in the two groups are similar and there would be no need for adjustment.
- The first approach is a complete randomized design; the second is a randomized complete block design.
- Similarly, we could block using “age groups”.

If we choose to “adjust for confounders” by analysis – via regression (complete randomized design); the concern is if data fit the model.

If we choose to “adjust for confounders by design – via stratified randomization (randomized complete block design), we would need two-way ANOVA (or even three-way ANOVA if adjusted for two confounders).

The term “treatment” may also mean different things; a treatment could be a factor or it could be multifactor. For example, let consider two different aspects of a drug regiment: Dose (Low, High) and Administration mode (say, one tablet a day or two tablets every other day). We could combine these two aspects to form 4 combinations; then treating them as 4 treatments and apply a complete randomize design. We call it a (balanced) Factorial Design; the analysis is similar to that of a randomized complete block design.

THE ROLE OF STUDY DESIGN

In a “standard” experimental design, a linear model for a continuous response/outcome is:

$$Y = \left[\begin{array}{c}\text{Overall}\\ \text{Constant}\end{array}\right] + \left[\begin{array}{c}\text{Treatment}\\ \text{Effect}\end{array}\right] + \left[\begin{array}{c}\text{Experimental}\\ \text{Error}\end{array}\right]$$

The last component, ‘experimental error”, includes not only error specific to the experimental process but also includes “subject effect” (age, gender, etc…). Sometimes these subject effects are large making it difficult to assess “treatment effect”.

Blocking (to turn a completely randomized design into a randomized complete block design) would help. But it would only help to “reduce” subject effects, not to “eliminate” them: subjects in the same block are only similar, not identical – unless we have “blocks of size one”. And that the basic idea of “Cross-over Designs”, a very popular form in biomedical research.

In the most simple cross-over design, subjects are randomly divided into two groups (often of equal sign); subjects in both groups/series take both treatments (experimental treatment and placebo/control) but in different "orders".

Group 1: Period #1 (Treatment) – washout – Period #2 (Placebo)

Group 2: Period #1 (Placebo) – washout – Period #2 (Treatment)

Of course, "order effects" and "carry-over effects" are possible. And the cross-over designs are not always suitable. They are commonly used when treatment effects are not permanent; for example some treatments of rheumatism.

DESIGNING CLINICAL TRIALS: NUTS & BOLTS OF THE BASICS

THE PROTOCOL

There are three fundamental aspects of trial design which must be precisely defined early in the planning phase:

(1)Which patients are eligible;

(2)Which treatments are evaluated;

(3)How each patient's response is to be assessed

These and other important details must be properly documented; writing this document, called "Study Protocol" is the most important first step – as mentioned in a previous lecture.

ORGANIZATION & FINANCE

Organizations for trials (Administration & Staff) are formed differently depending on sources of funding. Generally, there are three categories of trials:

(1) Investigator-initiated trials, under taken locally without external backing;

(2) Trials funded by federal grants and/or organized by nationally-based health organizations (e.g. cooperative groups such as ECOG);

(3) Trials organized by or with financial supports from pharmaceutical companies.

Local trials are usually small; statistical supports, for example, are provided by the institution.
Trials in groups 2 and 3 are often multi-center; DSMBs are required and statistical supports are organized and provided at trials' headquarter (for trials in group 3, that's the pharmaceutical company.
Pharmaceutical companies are responsible for organizing the great majority of clinical trials. The underlying purpose is for the company to obtain evidence regarding their product's efficacy and safety so that the product can get approved by FDA, can be successfully marketed, and make a healthy profit for the company.

THE ROLE OF A STATISTICIAN

It is a common mistake – even by statisticians – to assume that the statistician need only to be concerned with the analysis of results. The role of a statistician is more than a “data analyst”; of course the statistician plays the role as data analyst but, more important, he/she should also be involved during the whole process including the study’s design and conduct (trial monitoring). An experience statistician should be a “collaborating scientist” in ensuring that both protocol design and the interpretation of trial findings conform to sound principles of scientific investigation.

In addition, the statistician is often in a good position to act as an “ethicist”, a policeman in ensuring that satisfactory organizational standards are maintained throughout the trial.

PATIENTS

An important part of a trial is patients' selection. Any clinical trial requires a precise definition of which patients are eligible for enrollment. The early stage of protocol development may proceed with only a rough outline of the intended type of patient but, before the trial gets underway, this must be transformed into a detailed specification (to be included in the final protocol). The aspects to consider are:

(1) The disease under investigation;

(2) The source of patients

(3) Specific criteria for inclusion and exclusion

Selecting Participants:

In a clinical trial, inclusion and exclusion criteria, together, govern the selection process. The criteria for selecting participants should identify those who are likely to benefit and not be harmed by the treatment, easy to recruit, and likely to adhere to treatment and follow-up protocols. On the other hand, criteria also maximize our ability to generalize the findings from the trial to target population. For example, choosing only participants at high risk of an uncommon outcome can decrease sample size and cost, but may make recruitment more difficult and decrease our ability to general the findings.

INCLUSION/EXCLUSION

- Inclusion criteria: Patient characteristics required for entry, describing the population of patients that the drug is intended to serve. There are also exclusion criteria as well.
- For eligibility, consideration should be given to patients who are likely to benefit from treatment & to the generalization of the results:
  (i) Effectiveness of the treatment may be masked by the inclusion of patients with little chance of responding; (ii) On the other hand, with narrow criteria, generalization may be compromised.

Intervention and Control:

The choice and dose of intervention is a difficult decision that balances effectiveness and safety; other considerations include relevance to clinical practice, simplicity, suitable for blinding, and feasibility of enrolling subjects. These are often results of a long process of "early phase clinical trials". The best control group is a placebo control that allows participants, investigators, and study staff to be blinded. The strategy of using placebo compensates for any psychological effects so that any outcome difference between study groups can be ascribed to a biological effect.

Randomization and Blinding:

Randomization, which eliminates bias due to confounding variables, should be “tamperproof”. Thoroughly consider special randomization techniques: Blocked randomization, Stratified randomization, etc… Blinding the intervention is as important as randomization and serves to control bias through outcome ascertainment and adjudication. Consider “double blind”, “triple blind” features.

RANDOMIZATION

Randomization is a newer practice (1923) and has become the most basic feature of most modern-day designs; it helps to balance the characteristics we know as well as the characteristics we do not know or do not know how to quantify.

PATIEN REGISTRATION

For each patient who might be considered suitable, the following sequence of events should take place:

(1) Patient really requires/needs treatment
(2) Patient meets inclusion/exclusion criteria
(3) Both patient and clinician willing to accept randomization
(4) Patient consent is obtain (in writing)
(5) Patient entered the trial (enrollment)
(6) Treatment assignment obtained from randomization list

RANDOMIZATION STRATEGIES

Carefully consider all possibilities;
(1) Simple randomization
(2) Blocked randomization (block size, 2,3 or 4)
(3) Stratified randomization (Which patient factors one should stratify by? How many confounders? Define strata if a factor is on continuous scale)
Then a Randomization List is prepared (One master list or one list for each participating center?

UNEQUAL RANDOMIZATION

In a clinical trial with two treatments, it is standard practice to randomize roughly equal numbers of patients to each treatment. Equal-sized treatment groups provide the most efficient means of treatment comparison for any form of response (i.e. high statistical power). However, if the trial is comparing a new treatment against a standard, one maybe interested in gaining greater experience and insight into the new treatment's general profile; unequal randomization is a possibility. This might kame it worth considering even though it would involve some loss of statistical efficiency.

Randomization and Blinding both help reducing bias in treatment comparison.
Randomization deals with bias induced by founders.
Blinding deals with bias caused by human nature from participants in the trial.

THE DOUBLE-BLIND TRIAL

Potential sources of bias can sometimes be eliminated by ensuring that neither the patient nor those responsible for his/her care and evaluation know which treatment he/she is receiving. This is called the double-blind trial.

The term “double blind” is slightly misleading because in fact there are three types of blinded participants:

(1) Patients,

(2) Treatment team, and

(3) Evaluators

(1) The Patient: If the patient knows he/she is receiving a new treatment this may be of psychological benefit; in contrast, the patient knowing he/she is on standard treatment may react unfavorably especially being aware that other patients are "privileged to receive a new therapy.

(2) The Treatment Team: The patient's attending physician can affect the course of therapy in a number of ways. For example, if a patient is known to be receiving a new treatment, the physician may observe his/her progress more closely. The same potential bias applies to nursing staff.

(3) The Evaluators: It is important to ensure that those responsible for assessing patient outcome are as objective as possible. There is potential danger that evaluators will err towards more favorable responses on the new treatment if assignment known.

Some multi-center trials are “required’ to be triple-blinded; the third blinded component are members of DSMB, the independently-formed Data Safety and Monitoring Board (sometimes called DSMC, Data Safety and Monitoring Council)

BLINDING FEASIBILITY

For each trial, the following aspects should be carefully considered:

(1) Ethics: The double-blind procedure should not result in any harm or undue risk to a patient

(2) Practicality: For some treatment it would be impossible to arrange a double-blind trial

(3) Need: One needs to assess just how serious the bias might be without blinding; i.e. is blinding really needed?

VARIABLES

A set of decisions concerning the choice or choices of which variables to measure.

- Predictor or explanatory Variables
- Outcome Variables (primary, secondary)
- Confounders or Confounding Variables (and how to control them)

Measurements:

Clinically relevant outcome measures such as resolution of the disease/condition, pain, quality of life, occurrence/relapse of cancer, and death are the most meaningful outcomes of trials. Sometimes, investigators have choice but to rely on intermediary such as bone or breast density, HIV viral load. These intermediary markers are valid surrogate markers for clinical outcomes to the degree that treatment-induced changes in the marker consistently predict changes in the clinical outcomes.

All clinical trials should include measures of potential adverse effects of the intervention – even plan, called "Stopping Rule" to stop the trial when it goes wrong, as measured by these adverse effects.

Baseline Data:

Even though, in theory, randomization is supposed to eliminate the problem of confounding by factors that are present at the outset, and a lot of measurements adds expense and complexity, baseline data are important in many trials. If outcomes include change in a variable, the outcome variable must be measured at the beginning of the study in the same way that it will be measured at the end. And ones can check to see if randomization works well, or ones should back it up in the analysis – say, using “regression”.

SUBSEQUENT MONITORING

After getting approved and opened for operation, approved and open protocols are reviewed annually by a different regulatory body (often called Data Safety and Monitoring Board or DSMB) for progress made on accrual rate and progress toward study endpoints. Protocols determined to be unsafe (based on excessive adverse effects), to have inadequate accrual, to be without scientific progress, or have little likelihood of completion may be terminated based on committee vote. And, after a year or two, some studies might no longer be scientifically relevant.

If double-blind it not possible, sometimes partial blinding can be sufficient to reduce bias in treatment comparison; blinding the evaluators. This could be called “single-blind trial”

SOME TOPICS FOR BRIEF DISCUSSIONS

DESIGN AND VARIATION

Refer to this article:
Le C. T. Statistical comparison of two hand washing protocols.
Statistics in Medicine 5: 593-596, 1986.
Issue: Measuring outcome variable with less variation

DESIGN AND PRECISION

Refer this article:
Boissel, J.; Durieu, I., Girard, P.; Nony, P.; Chauvin, F.; Haugh, M. "Dose-Ranging Trials: Guidelines for Data Collection and Standardized Description." ***Controlled Clinical Trials*****, 16: 319 – 330, 1995**
(The dose-ranging experiments provide potency estimates, such as the Median Effective Dose (ED_{50}), of the potential new drug).
Issue: Why doses should be prepared to cover a wide range from very low to very high?

DESIGN AND EFFICIENCY

Refer to this article:
Le C. T. A new estimator for infection rates using pools of variable size. *American Journal of Epidemiology* 114: 132-136, 1981.

Issue: Pool testing for efficiency

Suggested Readings:

Search and learn about the structure and functions of Data Safety and Monitoring Board (DSMB; sometime called DSMC, “C” for Council).