What to do this week (Jan 19 and 24, 2023)?

Part I. Introduction

Part II. Epidemiologic Concepts and Designs

Part III. Clinical Trials

III.1 Clinical Trials: Introduction

III.2 Important Aspects in Study Design

III.3 Clinical Trial Conduct

III.4 Data Analysis

III.5 Statistical Monitoring

III.6 A Real-Life Clinical Trial: ACTG359

Part IV. Modern Biostatistical Methods

Part III.1 Clinical Trials: Introduction

- "Fundamentals of Clinical Trials" (4th Edition) by Friedman, Furberg and DeMets (FFDM2010)
- "Statistical Principles of Clinical Trials" (lecture notes) by Tsiatis and Zhang (TZ2012)

Two broad subject areas in the study of disease:

- **Epidemiology.** Systematic study of disease etiology (causes and origins of disease) using observational data (i.e. data collected from a population not under a controlled experimental setting).
- **Clinical Trials.** The evaluation of intervention (treatment) on disease in a controlled experimental setting.

Part III.1 Clinical Trials: Introduction

- **What Is a Clinical Trial?** a prospective, experimental study on intervention(s) in human beings
- **Why a Clinical Trial?** a powerful experimental technique, the most definitive method, for assessing the effectiveness of an intervention

Part III.1 Clinical Trials: Introduction

Historical perspective:

- Historically, the quantum unit of clinical reasoning has been the case history and the primary focus of clinical inference has been the individual patient. Inference from the individual to the population was informal.

- The advent of formal experimental methods and statistical reasoning made this process rigorous.

By statistical reasoning/inference we mean the use of results on a limited sample of patients to infer how treatment should be administered in the general population who will require treatment in the future.

Part III.1 Clinical Trials: Introduction

Pre-20th century medical experimenters had no appreciation of the scientific method. The notion of systematically collecting data to address specific issues was quite foreign.

An Example of Early Clinical Studies A common medical treatment before 1800 was blood letting: it was believed that you could get rid of an infection by sucking the bad blood out of sick patients; usually this was accomplished by applying leeches to the body. There were numerous anecdotal accounts of the effectiveness of such treatment for a myriad of diseases.

- Rush (1794): Treatment of yellow fever by bleeding

  "I began by drawing a small quantity at a time. ..."

- Louis (1834): A clear foundation for the use of the numerical method in assessing therapies.

Part III.1 Clinical Trials: Introduction

Pneumonia: Effects of Blood Letting

Days Bled after Onset	Died	Lived	Prop Surviving
1-3	12	12	50%
4-6	12	22	65%
7-9	3	16	84%

Louis (1835) studied the value of bleeding as a treatment of pneumonia, erysipelas and throat inflammation and found no demonstrable difference in patients bled and not bled.
This finding contradicted current clinical practice in France and instigated the eventual decline in bleeding as a standard treatment:
$\Longrightarrow$

- In 1827: 33,000,000 leeches were imported to Paris.
- In 1837: 7,000 leeches were imported to Paris.

Part III.1 Clinical Trials: Introduction

Modern clinical trials:

- the 1st clinical trial with a properly randomized control group was by the Medical Research Council, 1948

- 1950's the National Cancer Institute (NCI) organized randomized clinical trials in acute leukemia.
  Government sponsored clinical trials are now routine in USA.
  For example,

  - NIAID- (National Institute of Allergic and Infectious Diseases)
    Much of their funding now goes to clinical trials research for patients with HIV and AIDS.
    The ACTG (AIDS Clinical Trials Group) is a large cooperative group funded by NIAID. e.g. ACTG359

Part III.1 Clinical Trials: Introduction

Pharmaceutical Industry

- Before World War II no formal requirements were made for conducting clinical trials before a drug could be freely marketed.
- In 1938, animal research was necessary to document toxicity, otherwise human data could be mostly anecdotal.
- In 1962, it was required that an adequate and well controlled trial be conducted.
- In 1969, it became mandatory that evidence from a randomized clinical trial was necessary in USA to get marketing approval from the Food and Drug Administration (FDA).
- More recently there is effort in standardizing the process of drug approval worldwide. This has been through efforts of the International Conference on Harmonization (ICH). (http://www.pharmweb.net/pwmirror/pw9/ifpma/ich1.html)

Part III.1 Clinical Trials: Introduction

The great majority of the clinical trial effort is supported by the Pharmaceutical Industry for the evaluation and marketing of new drug treatments:

- The evaluation of drugs and the conduct, design and analysis of clinical trials depends heavily on sound Statistical Methodology
- This has resulted in an explosion of statisticians working for the Pharmaceutical Industry and wonderful career opportunities.

Part III.1 Clinical Trials: Introduction

Phases of Clinical Trials

- The process of drug development can be broadly classified as pre-clinical and clinical: experimentation that occurs before it is given to human subjects; whereas, with humans.

- We focus on only clinical research: assume that
  - the drug has already been developed by the chemist or biologist, tested in the laboratory for biologic activity (in vitro),
  - preliminary tests on animals have been conducted (in vivo)
  - the new drug or therapy is found to be sufficiently promising to be introduced into humans.

Part III.1 Clinical Trials: Introduction

Within the realm of clinical research, clinical trials are classified into four phases.

- Phase I: To explore possible toxic effects of drugs and determine a tolerated dose for further experimentation. [safety, tolerability]
  Also during Phase I experimentation the pharmacology of the drug may be explored.

- Phase II: Screening and feasibility by initial assessment for therapeutic effects; further assessment of toxicities. [feasibility, side effects and toxicity, logistics of administration and cost]

Part III.1 Clinical Trials: Introduction

- Phase III: Comparison of new intervention (drug or therapy) to the current standard of treatment; both with respect to efficacy and toxicity.
  [comparisons in efficacy and toxicity]

- Phase IV: (post-marketing) Observational study of morbidity/adverse effects.
  [something real, when in consumers' hands]

The definitions of the four phases are not hard and fast: many clinical trials blur the lines between the phases.

Part III.1 Clinical Trials: Introduction

Ethical Issues

Investigators and sponsors of clinical trials have ethical obligations to trial participants and to science and medicine.

- People have debated the ethics of clinical trials since the beginning.
- Ethical issues apply in all stages of a clinical trial.
  Conflicts between a physician's perception of what's good for his patient and for the design and conduct of the trial: the physician's obligations to the individual patient vs societal good?
- A well-designed trial should answer important public health questions without impairing the welfare of individuals.

Ethical considerations have given rise to many statistical challenges ...

Part III.2 Important Aspects in Study Design of Clinical Trials

- III.2.1 Developing Study Protocol
- III.2.2 Scientific Questions/Hypotheses
- III.2.3 Study Population
- III.2.4 Basic Study Design
- III.2.5 Randomization Process
- III.2.6 Sample Size

Part III.2.1 Developing Study Protocol

Every well-desgined clinical trial requires a protocol: a written agreement between the investigator, the participant, and the scientific community

Topic headings of a typical protocol (FFDM2010)

- A. Background of the study
- B. Objectives: primary, secondary question and response variables; subgroup hypotheses; adverse effects
- C. Design of the study: population; sample size; enrollment; intervention(s); follow-up visit schedule; ascertainment of response variables; safety assessment; monitoring; final analysis
- D. Organization: investigators; study administration
- Appendices: definitions of eligibility criteria, response variables; informed consent form; ...

Part III.2.2 Scientific Questions/Objectives

- The planning depends on the questions to be addressed: General objective is usally obvious but the specific question to be answered by the trial is often not stated well
  - define and write the question in advance, as specific as possible
  - intervention(s), response variable(s)

- Selection of Questions:
  - Each clinical trial must have a **primary question**: the one the investigators are most interested in answering and capable of being adequately answered
    - the sample size is determined upon it.
    - often it is framed in the form of testing a hypothesis, as an intervention is postulated to have a particular outcome: compared to the control, for example

Part III.2.2 Scientific Questions/Objectives

- There may also be a variety of subsidiary (**secondary questions**), related to the primary one.
  The study may be designed to help address them, or else data collected may also elucidate them:
  e.g. primary: whether mortality is altered by the intervension;
  secondary: incidence of cause-specific death, sex or age-specific mortality
- Important questions to be answered by clinical trials concern adverse events or side effects of therapy.
  It is not always possible to specify in advance the question to be answered: what adverse reactions might occur, and their severity, may be unpredictable.
- Ancillary questions, substudies

Part III.2.3 Study Population

The study population should be defined in advance, stating unambiguous inclusion (eligibility) criteria. The impact that these criteria will have on study design, ability to generalize, and participant recruitment must be taken into account. – FFDM2010

Definition of Study Population

Popultn at Large $\Rightarrow$ Popultn with Cond $\Rightarrow$ Study Popultn $\Rightarrow$ Study Sample

- Rationale.

  If an intervention is shown to be successful/unsuccessful, the medical and scientific communities must know to what kinds of people the findings apply. Plus, to assess the trial's merit and appropriateness, and to replicate the trial

Part III.2.3 Study Population

- Considerations.
  - Definition for eligibility criteria.
    the ones central to the study to be carefully defined.
  - Generalization.
    representativeness
  - Recruitment.
    the criteria's impact

Part III.2.4 Basic Study Design

Sound scientific clinical investigation almost always demands that a control group be used against which the new intervention can be compared. Randomization is the preferred way of assigning participants to control and intervention groups. – FFDM2010

- Randomized Control Trials.

  comparative studies with an intervention group and a control group; the assignment of a subject to a group is determined by the formal procedure of randomization.

  - removes the potential of bias in the allocation and produce comparable groups
  - guarantee the validity of statistical test of significance

Part III.2.4 Basic Study Design

- Nonrandomize Concurrent Control Studies.

  e.g. a comparison of survival results of patients treated at two institutes, one with the new surgical procedure and the other with a traditional care treatment

- Historical Controls and Databases.

  a new intervention is used in a series of participants and the results are compared to the outcome in a previous series of comparable participants: strengths vs limitations

- Cross-Over Designs.

  each participant to serve as his own control: e.g. two period cross-over design – each subject receives A or B in the 1st and the alternative in the succeeding period; the order in which A and B are given is randomized.

  A half in AB and the other in BA – wash-out period in between the periods?

Part III.2.4 Basic Study Design

- Withdrawal Studies.

  e.g. subjects on a treatment for a chronic disease are taken off therapy or have the dosage reduced, say, for duration benefit.

- Factorial Designs.

  e.g. to evaluate two interventions compared to control in a single experiment

Two by Two Factorial Design

	Intervention X	Control	marginals
Intervention Y	XY	CY	XY+CY
Control	XC	CC	XC+CC
marginals	XY+XC	CY+CC	
Effect of X: XY+XC vs CY+CC			
Effect of Y: XY+CY vs XC+CC			

Part III.2.4 Basic Study Design

- Group/Cluster Allocation Designs.

  if the intervention is most appropriately or more feasibly administered to an entire cluster

- Hybrid Designs.

  if a substantial amount of data from historical controls is available, to permit most study subjects to the new intervention

- Studies of Equivalency and Noninferiority.

  a new intervention has little/no superiority to existing therapies, but, as long as it's not materially worse, may be of interest becasue it is less toxic, less invasive, less costly, requires fewer doses, or improves QofL.

Part III.2.4 Basic Study Design

- Adaptive Designs.

  a great deal of interest: response adaptive

  e.g. a study, by design, will adjust the sample size to retain a desired power if the overall event rate is lower than expected, or the variability is higher than planned, or adherence is worse.

  e.g. a study with a formal stats monitoring
  more about it later .....

Part III.2.5 Randomization Process

Randomization tends to produce study groups comparable with respect to known as well as unknown risk factors, removes investigator bias in the allocation of participants, and guarantees that statistical tests will have valid false positive error rates. – FFDM2010

What is randomization in clinical trials?

The allocation of treatment to patients is carried out using a chance mechanism so that neither the patient nor the physician knows in advance which treatment will be assigned: each patient in the clinical trial has the same opportunity of receiving any of the treatments under study.

Part III.2.5 Randomization Process

Advantages of Randomization

- Eliminates conscious bias: physician selection; patient self selection
- Balances unconscious bias between treatment groups: supportive care; patient management; patient evaluation; unknown factors affecting outcome
- Groups are alike on average
- Provides a basis for standard methods of statistical analysis such as significance tests

Part III.2.5 Randomization Process

Design-based Inference

Randomization allows us to carry out design-based inference rather than model-based inference: the distribution of test statistics are induced by the randomization itself, rather than assumptions about a super-population and a probability model.

For example, we start by wanting to test the sharp null hypothesis: two treatments (A and B) would yield exactly the same response Y (the larger, the better) vs H_1: A is better.

- 4 patients are randomly allocated to A or B and their responses are observed: y_1, y_2, y_3, y_4; the test statistic $T = \frac{y_1^A + y_2^A}{2} - \frac{y_1^B + y_2^B}{2}$
- Under the sharp null hypothesis, the permutational probability distribution of our test static, induced by the randomization, can be evaluated:

Part III.2.5 Randomization Process

Permutational Distn Under H_0					
Patient	1	2	3	4	
Response	y_1	y_2	y_3	y_4	Test Statistic
Possible	A	A	B	B	$t_1 = \frac{y_1+y_2}{2} - \frac{y_3+y_4}{2}$
Treatment	A	B	A	B	$t_2 = \frac{y_1+y_3}{2} - \frac{y_2+y_4}{2}$
Assignments	A	B	B	A	$t_3 = \frac{y_1+y_4}{2} - \frac{y_2+y_3}{2}$
Each	B	A	A	B	$t_4 = \frac{y_2+y_3}{2} - \frac{y_1+y_4}{2}$
Equally	B	A	B	A	$t_5 = \frac{y_2+y_4}{2} - \frac{y_1+y_3}{2}$
Likely	B	B	A	A	$t_6 = \frac{y_3+y_4}{2} - \frac{y_1+y_2}{2}$

Suppose t_1 is observed, as $P_{H_0}(T = t_j) = 1/6$, we can calculate $p - value = P(T \geq t_1)$ by getting the proportion of $t_j \geq t_1$.

Part III.2.5 Randomization Process

Design-based Inference (cont'd)

To obtain the p-value, we conditioned on the individuals chosen in the experiment: we took their responses as fixed quantities. Randomness was induced by the chance assignment of treatments to individuals which in turn was used to derive the probability distribution of the test statistic.

What is the usual method? The usual statistical model which may be used in such an experiment: $Y_1, Y_2 \sim N(\mu_A, \sigma^2)$, and $Y_3, Y_4 \sim N(\mu_B, \sigma^2)$; to test $H_0 : \mu_A = \mu_B$ vs $H_1 : \mu_A > \mu_B$ with

$$T = \frac{\bar{Y}_A - \bar{Y}_B}{s_{pooled}[1/n_A + 1/n_B]^{1/2}} \sim t(n_A + n_B - 2)$$

Part III.2.5 Randomization Process

Comments about the permutation approach:

- The use of the permutational distribution for inference about treatment efficacy is limiting: ultimately, we are interested in extending our results from an experimental sample to some larger population.

- The importance of randomization is not the ability to validly use model free statistical tests as we have just seen; it is that it allows us to make causal inference. That is, the results of a randomized clinical trial can be used to infer causation of the intervention on the disease outcome.

  This is in contrast to non-randomized clinical trials or epidemiological experiments where only associational inference can be made.

Part III.2.5 Randomization Process

Disadvantages of Randomization

- Patients or physician may not care to participate in an experiment involving a chance mechanism to decide treatment

- May interfere with physician patient relationship

- Part of the resources are costed in the control group;

  If we had n patients eligible for a study and had good and reliable historical control data, then it is more efficient to put all n patients on the new treatment and compare the response rate to the historical controls.

How Do We Randomize?

Part III.2.5 Randomization Process

- Fixed Allocation Randomization

  assign interventions to the participants with a prespecified probability which is not altered as the study progresses

  e.g. assigning to A with prob π (and then, to B with $1-\pi$):
  $\bar{Y}_A - \bar{Y}_B$ with variance $\sigma^2[1/n_A + 1/n_B]$

  $\Longrightarrow \pi = 1/2$ to achieve the smallest variance

  - Simple Randomization
    e.g. generate $U_i \sim U(0,1)$ iid and then i to A if $U_i \leq \pi$
    advantages vs disadvantages

Part III.2.5 Randomization Process

- Blocked Randomization (or Permuted Block Randomization)

  staggered entry $\Longrightarrow$ imbalance of A vs B

  e.g. to choose a block size of 4, and within a block the order of treatment assignement is randomly permuted: AABB, ABAB, ..., BBAA

- Stratified Randomization

  define strata by breaking down our population into categories defined by different combinations of age and gender, say, and then within each stratum randomly allocate subjects

Part III.2.5 Randomization Process

- Adaptive Randomization

  the rule for allocation to different treatments may vary according to the results from prior patients already in the study.

  - Baseline Adaptive: to balance the allocation of patients to treatment overall and/or by prognostic factors.

    e.g. Efron biased coin design: D=3, $\phi = .25 < .5$; next assigned to A with prob $\pi_A = .5$ or ϕ or $1 - \phi$ if $|n_A - n_B| \leq D$ or $n_A - n_B > D$ or $n_A - n_B < D$, respectively.

Part III.2.5 Randomization Process

e.g. LJ Wei's urn model: m red balls and m blue balls; select one ball for a subject, red to A/blue to B; replace the selected ball with a different colored ball before the next selection.

e.g. minimization method by Pocock and Simon: when the total num of strata is large, consider a marginal discrepancy measure and minimize it by assigning the next treatment.

- Response Adaptive

  the responses of the past participants in the study are used to determine the treatment allocation for the next patient.

Part III.2.5 Randomization Process

e.g. play-the-winner rule (Zelen): First patient is randomized to either treatment A or B with equal probability, the next patient is assigned the same treatment as the previous one if the previous patient's response was a success; whereas, if the previous patient,s response is a failure, then the patient receives the other treatment.
The process calls for staying with the winner until a failure occurs and then switching.

e.g. urn model (L.J. Wei): The first patient is assigned to either treatment by equal probability. Then every time there is a success on treatment A, add r A balls into the urn; when there is a failure on treatment A add, r B balls. Similarly for treatment B. The next patient is assigned to whichever ball is drawn at random from this urn.

Part III.2.5 Randomization Process

Response adaptive allocation schemes have the intended purpose of maximizing the number of patients in the trial that receive the superior treatment.

Difficulties with response adaptive allocation schemes:

- Information on response may not be available immediately.
- Such strategies may take a greater number of patients to get the desired answer. Even though more patients on the trial may be getting the better treatment, by taking a longer time, this better treatment is deprived from the population at large who may benefit.
- May interfere with the ethical principle of equipoise.
- Results may not be easily interpretable from such a design.

Part III.2.6 Blindness

A clinical trial should, ideally, have a double-blind design in order to avoid potential problems of bias during data collection and assessment. In studies where such a design is impossible, other measures to reduce potential bias are advocated. – FFDM2010

Types of Blindness

- Unblinded (Open): both the participants and investigators know the identity of the intervention assignments.

  easy to conduct; some trials have to be so

- Single-Blind: only the investigators are aware of the identity of the intervention assignments.

Part III.2.6 Blindness

- Double-Blind: neither the participants nor the investigators responsible for following the participants/collection data/assessing outcomes should know the identity of the intervention assignments.
- Triple-Blind: in addition to the blindness of the participants and the investigators, the monitoring committee is not told the identity of the groups.

Some Practical Issues

- to protect the double-blind design
- matching of drugs: placebo
- coding of drugs
- unblinding: official, inadvertent
- assessment and reporting of blindness

Part III.2.7 Sample Size

Clinical trials should have sufficient statistical power to detect differences between groups considered to be of clinical importance. Therefore, calculation of sample size with provision for adequate levels of significane and power is an essential part of planning. – FFDM2010

One of the major responsibilities of a clinical trial statistician is to aid the investigators in determining the sample size required to conduct a study. – TZ2010

Part III.2.7 Sample Size

- Sample size determination/calculation is usually according to the primary objective.
- The specification of the required parameter values is usually based on historical information.
- Practical considerations: missing, limited resource

Sample Size Calculation Example. to compare the mean response between two treatments

- **formulation.**
  - Data to be collected: $Z_i = (Y_i, A_i)$ iid samples $i = 1, \ldots, n$

$$Y_i|A_i = 2 \sim N(\mu_2, \sigma^2), \quad Y_i|A_i = 1 \sim N(\mu_2 + \Delta, \sigma^2)$$

Part III.2.7 Sample Size

- **formulation.**
  - To test $H_0 : \Delta = 0$ vs $H_a : \Delta > 0$ with type I error (false positive) of rate α and power $1 - \beta$.
  - The test statistic to use is

$$T_n = \frac{\bar{Y}_1 - \bar{Y}_2}{\sigma(1/n_1 + 1/n_2)^{1/2}} \sim N(0, 1)$$

    under H_0 and $n_1 + n_2 = n$, assuming σ is known

Part III.2.7 Sample Size

- **to determine** n
  - to control the false positive: The rejection region is

$$\{(z_1, \ldots, z_n) : T_n \geq z_\alpha\}.$$

  - to achieve the power: $P_{H_a}(T_n \geq z_\alpha) \geq 1 - \beta$ and thus to determine n.
    - If specify $\Delta = \Delta_a > 0$ under H_a, the clinically important difference, and let $n_1 = n_2$, $T_n \sim N(\frac{\Delta_A}{\sigma(4/n)^{1/2}}, 1)$ and thus

$$\sqrt{n} \geq \frac{2\sigma(z_\alpha + z_\beta)}{\Delta_a}.$$

Note: $n \uparrow$ if $\sigma \uparrow$, or $\alpha, \beta, \Delta_a \downarrow$

Part III.2.7 Sample Size

Further Questions:

- What if σ is unknown? using s_{pooled}
- What if H_a is two-sided? using $z_{\alpha/2}$
- What if the distn of $Y|A$ is not normal?
  - using the MLE for the unknown mean and its asymptotic normality
  - using the exact distn when with small sample size
- What if to achieve a CI with certain length? the duality between testing and CI

Paractical Consideration:

- to account for potential missing?

What to study next?

Part III. Clinical Trials

- *Part III.1 Introduction*
- *Part III.2 Important Aspects in Study Design*
- **Part III.3 Clinical Trial Conduct**
  - **III.3.1 Recruitment of Study Participants**
  - **III.3.2 Data Collection and Quality Control**
  - **III.3.2 Assessing and Reporting Adverse Events**
- **Part III.4 Data Analysis**
  - **III.4.1 Baseline Assessment**
  - **III.4.2 Efficacy Assessment**
  - **III.4.3 Safety Assessment**
- *Part III.5 Statistical Monitoring*
- *Part III.6 A Real-Life Clinical Trial: ACTG359*