Homework 1 Review:

Read: Austin PC et al. J Clin Epidemiol. 2010 Feb;63(2):142-53. doi: 10.1016/j.jclinepi.2009.06.002.

Using the PBC dataset available at http://www.biostat.ucsf.edu.ucsf.idm.oclc.org/vgsm,

- *Describe the population to whom trial results apply.*
- *Following Austin's guidance, prepare "Table 1" for this trial.†*
- *Identify (i) the primary outcome, (ii) the intervention arms, and (iii) potential confounders.*
- *What strategies were employed to avoid bias?*

† Example 1: http://www.consort-statement.org/consort-statement/13-19---results/item15_baseline-data/
Example 2: http://www.nejm.org/doi/full/10.1056/NEJMoa012512#t=articleTop
Example 3: Ruel T, Kakuru A, Ikilezi G, et al. J Acquir Immune Defic Syndr. 2013 Dec 8.

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.

Assessment of Baseline Comparability

Item 15 of the CONSORT statement recommends that the investigators report baseline demographics and clinical characteristics of each group. This is typically done in the first table of a results paper.

Testing for Baseline Imbalance

Debate: Should one conduct formal statistical testing of baseline imbalances?

My opinion: No.

- Groups can never be shown to be identical. Only absence of "significant" differences can be demonstrated.
- A large number of statistical tests challenges our understanding of the meaning and importance of observed differences. If 5% of tests are significant, this is consistent with "chance."
- Identified imbalances do not invalidate a randomized trial, but they may make interpretation of results more complicated.
- Example: A nonsignificant baseline group difference in the history of hemorrhagic stroke could still affect the treatment outcome in thrombolytic trials.

What's important? To know which baseline factors may influence the trial outcomes – potential confounders.

- If these are imbalanced, does the direction of imbalance favor one group over the other?
- The critical baseline factors to consider ought to be prespecified in the protocol.
- The Discussion should comment on the effect of such baseline imbalances on the internal validity, as well as how the study population compares with patients seen in clinical practice.

Lecture 2

Learning Objectives:

Upon completion of this lesson, you should be able to do the following:

- Identify the research hypothesis and the corresponding study design
- Specify the experimental and control arms
- Specify the primary outcome
- Make sure these are in sync with each other and the study population

Homework 2 (due before class on Tue, Jan 21 – Mon, Jan 20 is a UCSF holiday):

1. Example 1:

   - Outcome: Prevent HIV seroconversion in women
   - Intervention: E = vaginal ring with ARV therapy; C = vaginal ring with placebo

2. Example 2: Select a trial from your own field and evaluate it similarly.

Questions:

1. How long should the intervention period be? What information will you use to determine this?
2. How will you capture the outcome data? Definition of outcome variable, including frequency of collection.
3. In what study sample could this trial be conducted ethically? Identify essential eligibility criteria that affect the Intervention-Outcome relationship.

Required Reading:

Robiner WN. Enhancing adherence in clinical research. Contemp Clin Trials. 2005 Feb;26(1):59-77.

Lecture 2

The Evidence Pyramid ranks studies with respect to strength of causal associations between an exposure and an outcome.

- The natural history of almost any disease and the variability of an individual's response to an intervention → need a control group.
- Random allocation of participants to study arms (experimental studies) provides stronger evidence than nonrandom allocation (observational studies).

Planning a clinical trial depends on the research question.

- An RCT should be designed with only one major question in mind.
- To encourage proper design and enhance the credibility of the findings, state the specific question clearly and prior to conducting the trial.
- Secondary questions also should be carefully selected, clearly defined, and stated in advance.

The primary question can be framed in the form of testing a hypothesis: the Arm-E mean level, μ_E, will differ from the Arm-C mean level, μ_C, by $\delta = \mu_E - \mu_C$.

$$H_0: |\delta| = 0 \text{ versus } H_A: |\delta| \neq 0, \text{ where } \delta = \mu_E - \mu_C .$$

[Do you see how both the exposure and the outcome are represented in these hypotheses?]

The anticipated causal relationship that prompted the research comparison is expressed via the alternative hypothesis.

- 'Not rejecting the null hypothesis' → Arm C should continue to be used in practice.
- 'Rejecting the null hypothesis' → Arm E should be used in place of Arm C.

	Intervention Groups		
Group mean	Arm C *[Control]* (N_C =)	Arm E *[Experimental]* (N_E =)	Difference
Estimated (Sample)	$\bar{y}_C$	$\bar{y}_E$	$d = \bar{y}_E - \bar{y}_C$
True (Population)	μ_C	μ_E	$\delta = \mu_E - \mu_C$

Since the research question addresses a causal association between an intervention and an outcome, the validity of the RCT rests on the quality of these variables.

- Intervention – Controlled by investigator:
    - Select the most relevant Control and Experimental conditions.
    - Deliver the allocated study arm to participants so that optimal exposure occurs and relative effectiveness (and safety) can be evaluated without bias. Specify intended 'exposure' in terms of how much (dose), how often (intensity), and how long (duration).
    - Verify performance: Were exposures received as planned?

- Outcome – Not controlled by investigator / Random variable:
    - Measure the outcome variable at a frequency that reflects the duration of the intervention effect.
    - Verify performance: Were outcomes measured and analyzed as planned?

Example from Homework 1: Knowler WC et al., 2002, N Engl J Med, 346(6):393-403.

Setting:

Treatment prevents some of the complications of type-2 diabetes but does not usually restore normoglycemia or eliminate all the adverse consequences.

Since current methods of treating diabetes remain inadequate, prevention is preferable.

The hypothesis that type 2 diabetes is preventable in persons at high risk for the disease

- is supported by observational studies and two clinical trials of diet, exercise, or both
- but not by studies of drugs used to treat diabetes.

Research Objectives:

- Does a lifestyle intervention or treatment with metformin, a biguanide antihyperglycemic agent, prevent or delay the onset of diabetes?
- Do these two interventions differ in effectiveness?

Questions:

1. How should the outcome measure be defined? What is the right follow-up period per participant?
2. How should interventions be defined?
   - What delivery processes should be put into place to ensure intended interventions are achieved?
   - What data monitoring (measures and processes) should be put into place to determine if intended interventions are achieved?

Outcome Measures … from their results paper

The primary outcome was diabetes, diagnosed on the basis of an annual oral glucose-tolerance test or a semiannual fasting plasma glucose test, according to the 1997 criteria of the American Diabetes Association:

- a value for plasma glucose of 126 mg per deciliter (7.0 mmol per liter) or higher in the fasting state, or
- 200 mg per deciliter (11.1 mmol per liter) or higher two hours after a 75-g oral glucose load.
- In addition to the semiannual measurements, fasting plasma glucose was measured if symptoms suggestive of diabetes developed.

The diagnosis required confirmation by a second test, usually within six weeks, according to the same criteria.

If diabetes was diagnosed:

- the participants and their physicians were informed,
- glucose-tolerance tests were discontinued (these require glucose intake, which is not safe among diabetics),
- fasting plasma glucose was measured every six months,
- glycosylated hemoglobin was measured annually.

As long as the fasting plasma glucose concentration was less than 140 mg per deciliter, participants were asked to monitor their blood glucose and to continue their assigned study treatment. *[Reason: Post-RCT observational study]*

If the fasting plasma glucose concentration reached or exceeded 140 mg per deciliter, the study medication was discontinued and the participant was referred to his or her physician for treatment.

Measurements of glucose and glycosylated hemoglobin (HbA_{1c}) were performed centrally.

All tests were performed without interrupting the assigned treatment, except that placebo or metformin was not taken on the morning of the test.

The investigators and the participants were unaware of the results of these measurements and were informed only if the results exceeded the specified threshold for a change in the treatment.

Follow-up duration (would reflect risk level of study pop'n)? Completeness of outcome collection?

Interventions

Eligible participants were randomly assigned to one of three interventions:

- standard lifestyle recommendations plus metformin (Glucophage) at a dose of 850 mg twice daily,
- standard lifestyle recommendations plus placebo twice daily, or
- an intensive program of lifestyle modification.

Medication arms:

- Standard lifestyle recommendations were provided in the form of written information and in an annual 20-to-30-minute individual session that emphasized the importance of a healthy lifestyle.
- Participants were encouraged to follow the Food Guide Pyramid[14] and the equivalent of a National Cholesterol Education Program Step 1 diet,[15] to reduce their weight, and to increase their physical activity.

Lifestyle arm:

- Participants were to achieve and maintain a weight reduction of at least 7 percent of initial body weight through a healthy low-calorie, low-fat diet and to engage in physical activity of moderate intensity, such as brisk walking, for at least 150 minutes per week.
- A 16-lesson curriculum covering diet, exercise, and behavior modification was designed to help the participants achieve these goals. The curriculum, taught by case managers on a one-to-one basis during the first 24 weeks after enrollment, was flexible, culturally sensitive, and individualized. Subsequent individual sessions (usually monthly) and group sessions with the case managers were designed to reinforce the behavioral changes.

Adherence

Medication arms:

- Adherence to the treatment regimen was assessed quarterly on the basis of pill counts and structured interviews.

Lifestyle arm:

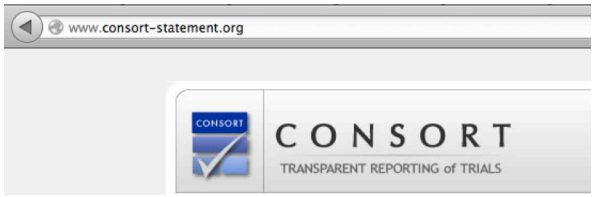
- *Monthly visits allowed monitoring of adherence?*

All arms:

- Self-reported levels of leisure physical activity were assessed annually with the Modifiable Activity Questionnaire.[16] The physical-activity level was calculated as the product of the duration and frequency of each activity (in hours per week), weighted by an estimate of the metabolic equivalent of that activity (MET) and summed for all activities performed, with the result expressed as the average MET-hours per week for the previous year.
- Usual daily caloric intake during the previous year, including calories from fat, carbohydrate, protein, and other nutrients, was assessed at baseline and at one year with the use of a modified version of the Block food-frequency questionnaire.[17]

Resources

ClinicalTrials.gov
A service of the U.S. National Institutes of Health



Study website: http://www.bsc.gwu.edu/dpp

Example 2: BVAIT Trial http://clinicaltrials.gov/ct2/show/NCT00114400?term=hodis&rank=4

Primary hypothesis:

> Daily vitamin B supplementation reduces progression of early atherosclerosis. The beneficial effects of vitamin B supplementation are expected to occur with or without a change in LDL-C levels.

Primary outcome:

> Ultrasonography will be used to measure the rate of change in the thickness of the carotid artery [at baseline and every 6 months for 2.5 to 4.5 years]

Secondary outcomes:

- CT will be used to measure coronary and aortic calcium [at baseline and end of study (2.5 to 4.5 years)]
- Neurocognitive change

Interventions: Participants will be randomized to receive, for 3.1 years, either

E = vitamin B supplementation consisting of folic acid 5mg, vitamin B12 0.4mg, and vitamin B6 50mg, or

C = a matching placebo.

CONCLUSIONS:

High-dose B vitamin supplementation significantly reduces progression of early-stage subclinical atherosclerosis (carotid artery intima media thickness) in well-nourished healthy B vitamin "replete" individuals at low risk for cardiovascular disease with a fasting tHcy >or=9.1 micromol/L.

Example 3: http://clinicaltrials.gov/ct2/show/record/NCT00390481

Marshall RS, et al. Cerebral hemodynamics and cognitive impairment: baseline data from the RECON trial. Neurology. 2012 Jan 24;78(4):250-5.

General Principles

Response Variables

Response variables are outcomes measured during the course of the trial that define and answer the questions. A response variable may be total mortality, death from a specific cause, incidence of a disease, a complication or specific adverse effect of a disease, symptomatic relief, a clinical finding, a laboratory measurement, or the cost and ease of administering the intervention. If the primary question concerns total mortality, the occurrence of deaths in the trial clearly answers the question. If the primary question involves severity of arthritis, on the other hand, extent of mobility or a measure of freedom from pain may be reasonably good indicators. In other circumstances, a specific response variable may only partially reflect the overall question. As seen from the above examples, the response variable may show a change from one discrete state (living) to another (dead), from one discrete state to any of several other states (changing from one stage of disease to another) or from one level of a continuous variable to another. If the question can be appropriately defined using a continuous variable, the required sample size may be reduced. However, the investigator needs to be careful that this variable and any observed differences are clinically meaningful and relevant and that the use of a continuous variable is not simply a device to reduce sample size.

In general, a single response variable should be identified to answer the primary question. If more than one are used, the probability of getting a nominally significant result by chance alone is increased. In addition, if several response variables give inconsistent results, interpretation becomes difficult. The investigator would then need to consider which outcome is most important, and explain why the others gave conflicting results. Unless she has made the determination of relative importance prior to data collection, her explanations are likely to be unconvincing.

From a statistical viewpoint, every randomized participant should be included in the analysis. Consequently, the investigator must keep trying to get all participants back for scheduled visits until the trial is over. Even if a participant is taken off the study intervention by an investigator or stops taking it, he should be encouraged to come in for regular study visits. Complete follow-up data on the response variables are critical to answering the research question.

Intervention variable: Planned exposures – experimental and control

When the question is conceived, investigators, at the very least have in mind a class or type of intervention. More commonly, they know the precise drug, procedure, or lifestyle modification they wish to study. In reaching such a decision, they need to consider several aspects.

- First, the potential benefit of the intervention must be maximized while possible toxicity is kept to a minimum.
  - Dose of drug or intensity of rehabilitation and frequency and route of administration are key factors that need to be determined.
  - Can the intervention be standardized, and remain reasonably stable over the duration of the trial?
  - Investigators must also decide whether to use a single drug, biologic, or device, fixed or adjustable doses of drugs, sequential drugs, or drug or device combinations.
  - Not only the nature of the intervention, but what constitutes the control group regimen must also be considered for ethical reasons and study design reasons.

- Second, the availability of the drug or device for testing needs to be determined. If it is not yet licensed, special approval from the regulatory agency and cooperation or support by the manufacturer are required.

- Third, investigators must take into account design aspects, such as:
  - time of initiation and duration of the intervention,
  - need for special tests or laboratory facilities, and
  - the logistics of blinding in the case of drug studies.

  Duration of intervention effects (acute / chronic): Certain kinds of interventions, such as surgical procedures, device implantation, vaccines, and gene transfer may have long-term or even life-long effects. Therefore, investigators might need to incorporate plans for long-term assessment.

Intervention variable: Achieved exposures

- What can be done before enrollment to reduce future adherence problems?
- How to maintain good adherence during a trial?
- How to monitor adherence?
- How to deal with low adherence.

A. Controlling adherence / Preventing low adherence

The terms compliance and adherence are often used interchangeably.

- Compliance is "the extent to which a person's behavior (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice."
- Adherence is defined similarly, but implies active participant involvement. An adherer is a participant who meets the standards of adherence as established by the investigator.

Many potential adherence problems can be prevented or minimized before participant enrollment.

- Study population: Avoid enrolling participants likely to have low adherence.
  - A run-in period can be useful – to identify low adherers, those more likely to benefit from the intervention, and those more likely to suffer from the intervention.
  - Typically ineligible: Low literacy / cognition / self-efficacy; concomitant diseases; not projected to remain available throughout intervention and follow-up period.
  - Consent process indicates understanding of and commitment to trial goals: Participate as study partner; support of family members
- Limit design features that may adversely influence the level of adherence.
  - Study duration: Longer f'up period risks lower adherence.
  - Simplicity of intervention: Opportunities for PT-2-PT variation reduce comparability among participants (e.g., diet prepared at home vs. food supplied by study).

Once a participant is enrolled, taking measures to enhance and monitor participant adherence is essential.

- Foundation: A well-functioning setting with committed clinic staff.
- A positive experience at the first contact with future participants is a worthwhile investment: satisfied participants are better adherers. This approach includes: trusting interactions, adequate time to discuss complaints, demonstration of sincere concern and empathy when appropriate, convenient clinic environment, short waiting times, etc.
- Reminders can also reduce the risk of low adherence. Asking a participant about the best time and mode of contact is usually appreciated.
- Any discussion of low adherence should not be confrontational.

Ref: Shumaker SA, Ockene JK, Riekert KA (eds.). The Handbook of Health Behavior Change (3rd edition). New York: Springer Publishing Company, 2009.

B. Monitoring and quantifying actual exposure

- Monitoring adherence is important in a clinical trial for two reasons:
  - first, to identify any problems so that steps can be taken to enhance adherence;
  - second, to be able to relate the trial findings to the level of adherence.
- A measure of study quality: Is it replicable and portable? Only so if interventions are too.
- Measuring adherence is easy for one-time interventions.
- For long-term trials,
  - Frequent determinations have more value than infrequent ones: yield a better indication of true adherence; prompt participant that he is being monitored, which may encourage adherence; allow corrective action to be taken when low adherence is noted.
  - Pills: Pill counts at study visits; electronic caps (how often opened?); special pill boxes help the participant keep track of when to take the medication; participants with dosing problems are more likely to become permanent drop-outs
  - Physiologic measures: Drug levels;
  - Food: Diaries (24-hr recall); Smartphone apps allow real-time tracking

C. Analyzing actual exposure

In general, analysis of trial outcomes by level of adherence is strongly discouraged. However, if the control and intervention groups are not being treated as intended,

- Group differences may be diluted, leading to underestimates of efficacy and harm.
- Differential adherence can lead to biased conclusions. The actual level of adherence can be compared with what was expected when the trial was designed.

A realistic estimate of the adherence level during a trial allows proper upward adjustment of the target sample size during the planning phase. Data from a meta-analysis suggest that the difference in health benefits between high and low adherence is 26%. Given the intention-to-treat principle of analysis, in order to maintain equivalent power,

- 20% reduction in adherence may result in the need for 1.5-fold increase in sample size and
- 30% reduction will require doubling of the study cohort.

Reference for today's lecture:

Fundamental of Clinical Trials, 4th edition. Lawrence Friedman, Curt Furburg, David DeMets.
eBook is available online to UCSF community.