Cornfield on research

On being asked to talk on the principles of research, my first thought was to arise after the chairman's introduction to say, “be careful” and to sit down.

Source: Cornfield, *Am J Ment Defic* 64:240-252, 1959

Study endpoints

(Source for this section: Piantadosi, *Clincial Trials*, 1997)

- Endpoints are commonly referred to as outcomes and they come in many different varieties.

- Endpoints are at the experimental unit level and are used to assess the study objectives

Clarity and precision of these definitions is key:

For example, a study objective of "improved survival" might mean prolonged median survival, higher five-year survival, or a lower death rate during the first year. Moreover, what type of survival is relevant: Overall or disease-specific?

'Hard' endpoints are preferred; i.e. clinical landmarks that are well defined in the study protocol, definitive with respect to the disease process, and require no subjectivity.

'Soft' endpoints are those that do not relate strongly to the disease process or require subjective assessments by the investigator or patient. (e.g. pain)

Surrogate endpoints are endpoints that are measured in place of the biologically definitive or clinically most meaningful endpoint.

A definitive endpoint measures clinical benefit, whereas a surrogate endpoint is one that tracks the progress or extent of the disease.

Obviously, a good surrogate endpoint needs to be convincingly associated with a definitive clinical outcome so that it can be used as a reliable replacement.

Some commonly used surrogate endpoints are CD4+ counts for AIDS, tumor size reduction for mortality, PSA level for disease progression, blood pressure and cholesterol level for Hemorrhagic stroke or myocardial infarction.

Composite endpoints are simply combinations of multiple endpoints. (e.g. follow until Stroke or MI)

(For example: Endpoint = any increase in Blood pressure + #MIs + #Strokes).

Randomization and balance

(Source for this section: Meinert CL: Design and Conduct of Clinical Trials Course slides, 1994)

Random (Lay definition): Having no specific pattern or objective; lacking causal relationships; haphazard.

Random (scientific definition): A selection or assignment process in which there is associated with every legitimate outcome a know probability.

Randomization - The actual process of carrying out a random selection or assignment procedure.

Randomization only provides a reason why the sample is more likely to be balanced with respect to unknown covariates than unbalanced.

Randomization only implies balance on average, so each data set must be assessed for imbalance and analyses must be adjusted accordingly.

Reasons for random treatment assignment

- Eliminate selection bias w.r.t. treatment assignment
- Provide study groups with known statistical properties regarding baseline composition
- Expected degree of baseline comparability for an unobserved variable is the same as for an observed variable

Misconceptions regarding randomization

- A haphazard procedure is the same as a random procedure
- Randomization ensures comparable study groups
- Differences in the baseline composition of the study groups is evidence of a breakdown in the randomization process
- It is possible to test for “randomness”
- A study that does not involve random treatment assignments is invalid

The intention to treat (ITT) principle

The ITT principle provides a guideline for defining the treatment groups to compare in the statistical analysis.

The ITT says that patients should be grouped and analyzed according to the treatment that they were randomly assigned to, regardless of whether they actually received, or complied with, that treatment.

By contrast, ‘as-treated’, ‘complier’, or ‘treatment received’ analyses group patients according to what treatment they actually received or complied with.

An important property of the ITT is that it “preserves the randomization” while the ‘as-treated’ analysis does not.

“Preserving the randomization” means that the benefits of randomization still apply. That is, it is still more likely that the treatment groups are approximately balanced with respect to unknown confounders than unbalanced.

Treatment received analyses are particularly susceptible to confounding from unknown confounders (such as disease severity).

Generalizability

The generalizability of a study is given, almost exclusively, by the patient population, treatment procedure and procedure of the clinical trial. Note that this is a scientific concept and not a statistical one.

Considerations

- Homogeneity versus Heterogeneity
- Select versus representative population
- 'Real world' versus experimental setting
- Desired population mix with regard to demographic factors
- Presumed treatment mechanism
- Method of determining eligibility
- Randomization does not imply generalizability

Generalizability should not be confused the **validity** of a study, which refers to the conduct and reproducibility of the study itself.

Myths of clinical trials

(Slides Adapted from:
Curtis L Meinert, PhD; Hopkins school of Public health)

Definition of Myth:
A popular belief that is false or baseless

Myth #1
That being in a trial is akin to being a guinea pigs

Myth #2
Only those receiving the test treatment will benefit

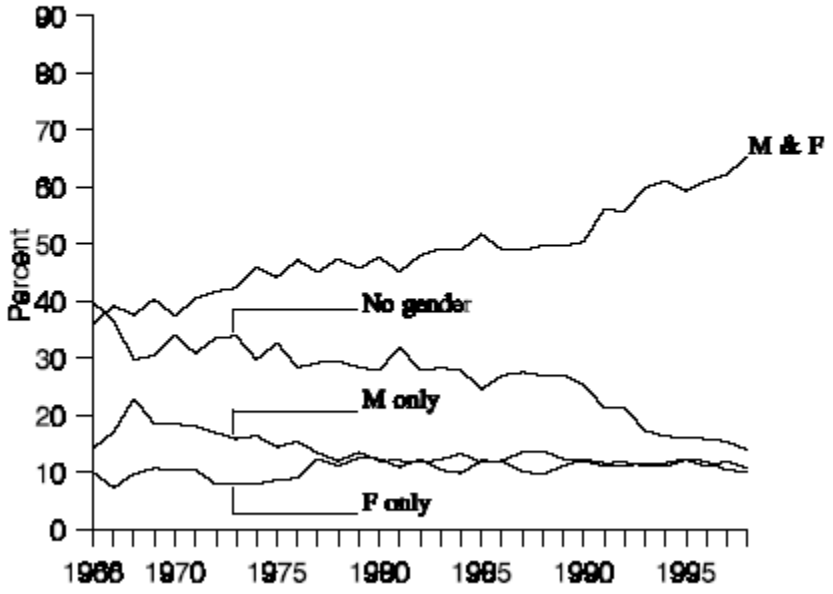
Myth #3
That placebos have no effects

Myth #4
That people enroll in trials because they expect to benefit

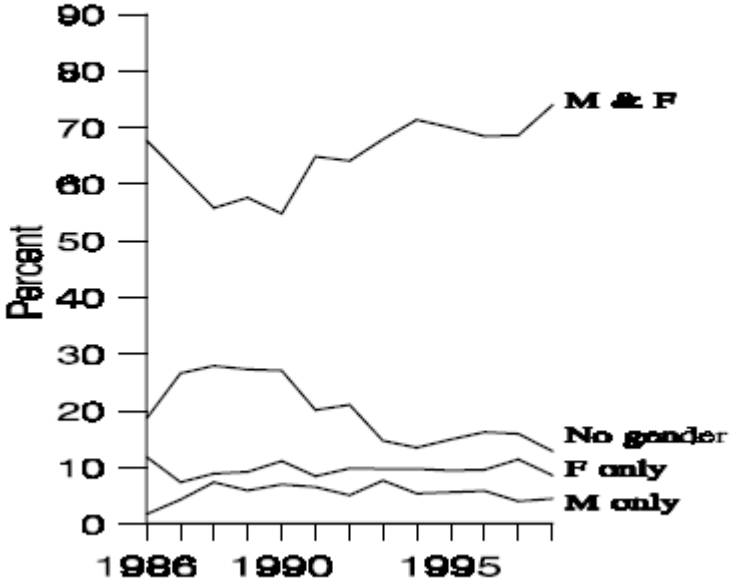
Myth #5
That selection bias matters

Myth #6
That trials have concentrated on men and their diseases to the exclusion of women and their diseases

Published trials by gender



Published multicenter trials by gender



Myth #7
That "representativeness" is possible

Myth #8
That validity depends on "representativeness"

Myth #9
That generalization depends on "representativeness"

Myth #10
That randomization ensures comparability

Myth #11
That data can be spoiled by looking at them

Myth #12
That p-values indicate significance

Myth #13
That subgroup analysis is a sin

Myth #14
That masked trials are better than unmasked trials

Myth #15
That the monitoring body should be isolated from study investigators

Myth #16
That monitoring bodies should be masked

Myth #17
That monitoring must be according to pre-ordained stopping rules

Myth #18
That truth can be revealed by a single trial

Myth #19
That investigators are not to be trusted

Myth #20
That anybody can do a trial

And Finally:
Myth #21
That trials change the practice of medicine