THEORY AND GOALS OF RANDOMIZATION IN CLINICAL TRIALS

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“Let us take out of the Hospitals, out of the camps, or from elsewhere, two hundred, or five hundred poor people, that have fevers, pleurisies, etc. Let us divide them into halfes, let us cast lots, that one halfe of them may fall to my share, and the other to yours; I will cure them without bloodletting and sensible evacuation; but do you do, as ye know...We shall see how many funerals both of us shall have.”

Van Helmont, 1662
THE CONCEPT OF RANDOMIZATION

- Introduced into agricultural experiments in 1920’s by R.A. Fisher, a British geneticist and the father of experimental design.
- Fisher recognized that testing soil treatments, etc., on systematically selected plots left it to the investigator’s judgment to “balance” for all other factors that might affect outcome.
- Randomization permitted assumption that there were no differences between treatment groups--except for the treatment itself.
In 1940’s, British statistician Austin Bradford Hill, very familiar with confounding issues from his work in occupational epidemiology, pushed for randomization in clinical trials funded by the Medical Research Council. Hill:

“...having used a random allocation, the sternest critic is unlikely to say when we eventually dash into print that quite probably the groups were differentially biased through our predilections or through our stupidity.”
EFFECT OF RANDOMIZATION

- Can assume prognosis is approximately the same on average in each randomized group
- For factors that you know are prognostic, and are measured, you can check on balance across groups
- For factors that you don’t know about, randomization allows you not to worry
EFFECT OF RANDOMIZATION

Good Prognosis

Poor Prognosis

R A N D O M I Z E

Treatment A

GP

PP

Treatment B

GP

PP
ETHICAL JUSTIFICATIONS
PROPOSED FOR RANDOMIZATION

- **Equipoise**
  - Physician has no preference for either treatment

- **Clinical equipoise**
  - Physician may have preference but recognizes there are differing views

- **“Uncertainty Principle”**
  - Both physician and patient are uncertain as to which treatment might be more beneficial
RANDOM ≠ HAPHAZARD

- Alternating assignments: not randomization
RANDOM ≠ HAPHAZARD

- Alternating assignments: not randomization
- Assigning treatment according to first letter of last name: not randomization
RANDOM ≠ HAPHAZARD

- Alternating assignments: not randomization
- Assigning treatment according to first letter of last name: not randomization
- Assigning treatment according to day of arrival at clinic: not randomization
Alternating assignments: not randomization
Assigning treatment according to first letter of last name: not randomization
Assigning treatment according to day of arrival at clinic: not randomization
Assigning treatment according whether day of birth is odd or even: not randomization
HOW TO UNDERMINE RANDOMIZATION

- Inadequate concealment of treatment assignment
  - If trial personnel know treatment to be assigned, may affect who gets approached to be offered trial participation
HOW TO UNDERMINE RANDOMIZATION

- Do not bother to follow up randomized participants who stop taking study medication
  - Prognosis of those stopping treatment may differ from those who remain compliant, and this difference may not be the same for both treatment arms
HOW TO UNDERMINE RANDOMIZATION

- Allow those who evaluate outcomes be aware of treatment assignment
  - If evaluators believe one treatment is better, may affect their judgment of which events meet criteria and which do not
RANDOMIZATION IN STANDARD OF CARE TRIALS

- Such trials are likely to be heterogeneous in many ways
- Heterogeneity makes “signal” more difficult to detect
- Especially critical to avoid even small biases that can hide a small (but important) effect, or produce an apparent (but false) effect
SOME PROPOSED MODIFICATIONS TO RANDOMIZATION PROCESS
In most trials, allocation ratio (usually but not always 1:1) is consistent throughout the trial. Some advocate a “response-adaptive” approach to randomization:

- Change the allocation ratio as trial progresses to favor the treatment that is looking better.
- Goal: end up with more participants receiving the superior treatment.
- Several such approaches have been proposed:
  - “Play the Winner”
  - Adaptive biased coin designs
  - Urn designs
ISSUES WITH RESPONSE-ADAPTIVE RANDOMIZATION

- Patient characteristics may change over time; may end up with imbalances
- Imbalanced allocation is less efficient; will need a larger trial, offsetting reduction in actual number getting inferior treatment
- Once you have formally determined that one treatment is likely superior, is it ethical to continue randomizing at all?
TIMING OF RANDOMIZATION

- Randomized consent design, also known as pre-randomization
  - Determine eligibility and obtain random treatment assignment prior to consent
  - Originally proposed for comparisons of new treatment to standard of care; those randomized to standard of care would not be informed they were included in study
  - To maintain validity of analysis, must analyze according to treatment assigned, regardless of whether patient accepted that treatment
  - Motivation: belief that patients more likely to agree to participate in trial if they are told what they will get

- Cluster-randomized trials, in which treatment assignment will be known in advance for all in cluster, has some similarities to randomized consent design
ISSUES WITH RANDOMIZED CONSENT DESIGN

- No allocation concealment; may affect which patients are approached to participate in study
- Knowledge of assigned treatment may substantially affect information provided during consent process
  - Over-focus on benefits of assigned treatment, minimization of risks
  - Physician may not reveal that treatment assignment was chosen randomly
- Selection bias: some individuals will refuse assigned treatment
- In practice has usually not led to the hypothesized large increases in accrual