Lecture 3
Biostatistics III: Clinical Trials

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Equipoise

Blinding

Randomization

The Point

Equipoise

"a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial. "

Equipoise and the ethics of clinical research.
N Engl J Med. 1987 Jul 16;317(3):141-5.
Freedman B.

Freedman continues

"I suggest an alternative concept of equipoise, which would be based on ... controversy in the *clinical community* over the preferred treatment. According to this concept of 'clinical equipoise,' the requirement is satisfied if there is genuine uncertainty within the *expert medical community* — not necessarily on the part of the individual investigator — about the preferred treatment. "
(Emphasis mine)

Personal Equipoise

Personal Equipoise $\neq$ Clinical Equipoise

Just because you are sure that a treatment is better does not mean there is not clinical equipoise. If you didn't at least think the treatment was better you would likely not be running the trial.

Clinical Equipoise

Clinical equipoise means that there is genuine uncertainty in the expert medical community over whether a treatment will be beneficial as compared to standard of care.

Loss of Clinical Equipoise

Before there are any treatments, equipoise must only exist between a placebo and the untested treatment.

Once the accumulation of experimental evidence has removed the clinical equipoise between a treatment and placebo, that treatment becomes the standard of care.

Once you have a standard of care you must ethically provide that to all subjects in your trial. There are ways around this - next lecture.

Lack of Personal Equipoise

Because personal equipoise is not required - it causes bias!

- Study Team changes data to make it look better
- Doctors treat subjects in the different arms differently
- Follow-up is different between the two arms

Why Blind

- Lack of personal equipoise
- Placebo effect
- People that know they are on active treatment complain more
- Academic reward systems create an inherent conflict of interest
- To be human is to have bias
- To avoid any appearance of bias

1-2-3

The triple blind!

- Blinding subjects to what they are receiving - placebo effect
- Blinding treating MDs - so they don't treat patients differently
- Blinding the study team - so they don't make decisions that bias the results of the trial
- Blinding the study team - so they can't change data

Forced Equality

If no one knows what treatment a patient receives, they are forced to treat everyone the same. This eliminates as much conscious and unconscious bias as possible and is the single most effective way to eliminate bias other than randomization.

Why people don't blind

- Known side effects of treatments need to be balanced
- Blinding takes thought and often manufacturing of a placebo that looks the same as the treatment is not feasible
- Some things can't be blinded, but there are sham surgeries!
- Unblinded study team members cannot be involved in running the trial - or must be a soulless robot - always me.
- Requires a governing group that gives advice to save the blind if unexpected problems occur

The Slow Mouse Example

Some things that seem random are not!

Remove yourself from the randomization

Coin Flipping

Binomial randomization

- super easy
- each subject randomized on the spot as they arrive
- each subject has the same probability of begin randomized to treatment or control
- neither gives a set number randomization nor ensures balance in a finite sized trial
- generally eliminates time trend problems, but possibly not

Fixed Hat Picking

Block randomization

- Requires prior planning
- Gives a set number randomization and ensures balance
- Eliminates time trend problems
- Some fixed blocks can be broken, random blocks cannot

When you shouldn't randomize

Very small samples should be matched not randomized. Randomization only eliminates bias in infinite samples...and it helps with everything we can't measure in larger finite samples.

No randomization is perfect, looking at the balance in the arms by known precision variables and baseline characteristics after the fact is always a good idea.

Stratification

Since randomization isn't perfect, randomization should be stratified by known risk factors or precision variables (something related to outcome but not treatment) whenever possible.

all this means is you randomize within each group separately. For example - stratification by village, you randomize within village separately. stratification variables should be adjusted for/ stratified by in the analysis to increase power! You know it is not a confounder, so this will just increase precision.

Clear Answers

The point of blinding and randomization is to obtain clear answers that are convincing to the largest number of people.

The Moral Imperative to Get a Clear Answer

Volunteers must be protected whenever possible. Compromising the validity of the trial conclusions is also unethical.

Compromising the validity of the trial conclusions is the same as putting all the volunteers at risk for no reason. Clinical trials have inherit risk, this is why we have informed consent. There must be a balance between protecting volunteers and protecting the scientific validity of conclusions.