Lecture 2
Biostatistics III: Clinical Trials

Michael C Sachs

Translating a Hypothesis to an Objective

Endpoints and Outcomes

The Population and The Sample

Hypotheses of Treatment Intervention

The treatment will cause an **individual's** outcome to be

- better, than
- worse than, or
- about the same

than if they received

- placebo
- current standard of care or
- some other experimental treatment
- something that always makes their outcome Q

We can't know this!

We can never know what would have happened for a given individual:

- We can only know what happened to an individual in one reality at one time
- The unobserved realities produce *counterfactual* outcomes
- If we could observe the counterfactuals, we could answer the question everyone wants to ask

....but we cannot.
The best we can do is look at some group's summary outcome and compare to the other group's summary outcome.

Translation 1

The treatment will cause the group receiving it to have outcomes that are

- higher
- lower
- about the same

than a comparable group receiving

- placebo
- current standard of care or
- some other experimental treatment
- something that makes everyone's value Q

Translation 2

The treatment will **tend** to cause the group receiving it to have outcomes that are **on average**

- higher
- lower
- about the same

than **the average outcome** in a comparable group receiving

- placebo
- current standard of care or
- some other experimental treatment
- something that makes everyone's value Q

Translation 3 - Final

Determine if the treatment will **tend** to cause the group receiving it to have outcomes that are **on average** the same as the **the average outcome** in a comparable group receiving placebo.

Hypothesis vs Objective

Some statisticians/PI treat these as the same thing...and they are close...I do not!

- A hypothesis contains a judgement or prediction
- An objective states the things to be determined
- They can be extremely close - depends on how specific you would like to be in your hypothesis.
- Hypothesis can be much less specific

Example from above

hypothesis a:
The treatment will tend to cause the group receiving it to have outcomes that are higher than a comparable group receiving placebo.
hypothesis b:
The treatment will cause better outcomes on average as compared to placebo.
hypothesis c:
The treatment causes increased outcomes on average as compared to placebo.

Objective:
To determine if treatment will tend to increase outcome measurements in the treatment group over the outcome measurements in the placebo group.

A study needs an Objective

But also benefits from the hypothesis
The objective is the full translation of the original hypothesis. The hypothesis is your opinion on which way the evidence from the objective will turn out.

You should always state your hypothesis, as well as the objective!

Hard Outcomes

Hard outcomes of interventional trials

- survival/death and time to death
- disease cure and time to disease cure
- infection and time to infection
- injury and time to injury
- quality of life

Soft Outcomes

Examples of soft outcomes

- blood pressure reduction for a blood pressure medication
- pathologic response for a cancer treatment
- blood level of tobacco in tobacco cessation treatment

Surrogate outcomes

Examples of Potential surrogate outcomes

- self-report of condom use for a HIV prevention intervention
- ELISA titers for a HPV vaccine
- direct skin feed measurements for a transmission blocking malaria vaccine

Examples of validated surrogate outcomes

- HZV titer increase from baseline to 6 weeks post last vaccination for ZosterVax
- Absolute HBV Titer level for HBV vaccines

Hard >>validated surrogate>Soft endpoint

Soft endpoints and surrogates are very often used in Phase II trials, where you simply want to look at activity.

However, surrogates should be **validated** i.e. treatment effects on them have been shown to reliably predict treatment effects on the clinical outcome. Soft endpoints should be considered in the causal pathway of the intervention or a summary of a hard endpoint, but may not predict the efficacy.

Example and the grey area

You have found that an intervention increases bone density in animals and you believe it will help prevent bone breakage in women with a history of osteoporosis by increasing bone density. After running a dose and safety phase I trial, you want to run a phase II trial.

Are the below potential surrogates, soft endpoints or hard endpoints?

- Changes in bone density
- Calcium levels in the blood
- Hours walked per-week

You run the phase II and find activity,

What is your hard endpoint?

- time to break or number of breaks
- quality of life (how do you measure that?)
- Death

Example and an even grayer area

A T-cell/B-cell HIV vaccine has passed phase I trials,

What is your phase II endpoint?

- ELISA titers B-cells
- T-cell responses
- Some mixture of the above and how

You run the phase II and find activity for Elisa titers but not T-cells,

What is your hard endpoint?

- HIV infection or time to infection
- Disease
- Death
- Secondary infection

What if the vaccine doesn't change infection rates at all, but makes everyone who becomes infected long-term non progressor or even functionally cured without treatment?

The population should always be stated

The population is the group of people you want the subjects you use in your trials to be generalizable to. This is ALL of the people you want to be able to use your intervention or diagnostic test or device.

When picking a sample

- Ideally you want a random sample from that population.
- in reality reduce the bias in your sample as compared to the population as much as possible

In truth no samples are 100% unbiased because subjects that are willing to be in a clinical trial not representative of the population of interest. However, clear biases should be avoided or should be noted when reporting the results.

Avoiding Bias - Example

You want your treatment to be available for all women with osteoporosis - All women with osteoporosis is your population.

Clear biases

- Using men in the study
- Using only white women in the study
- Using healthy subjects in your study
- Using only women above the age of 75 or only with severe osteoporosis
- Restricting the general health of women enrolled (although this is often done on some level for safety reasons)

Somethings cannot be helped and once disclosed are considered unimportant.

Unavoidable Bias - Examples

- Location:
Many clinical trials are run in Seattle, Washington, because of the facilities there. However the treatments found are used all over the world. This could be a problem if the facilities or Seattle in general allow for a much greater effectiveness of the treatment, but this is generally ignored as a bias.

- Willingness to volunteer:
As mentioned above people willing to be in a clinical trial are not like everyone else in many cases. E.g., black Americans, Roma in EU, are often distrustful of medical experimentation.

- Minimal health criteria:
You don't want to kill anyone in your trial, so you don't let subjects with poor general health in the trial. However the treatment, once cleared, will generally not be restricted to the healthy.