Lecture 1
Biostatistics III: Clinical Trials

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Learning Objectives and Resources

The Scientific Method

Types of Medical Studies

Evidence Supporting a Hypothesis versus Hypothesis Generating

Goals for Today

By the end of today you should know:

1. The Scientific Method
2. The differences between evidence supporting a hypothesis and hypothesis generating information
3. How to link a simple hypothesis in words to an objective that can be tested
4. How to pick a good endpoint
5. About clinical equipoise
6. Why we blind
7. Why we randomize
8. The very basics of simple trial design
9. How to ask for help to design a more complicated trial

Order and hopeful Timing

- Lecture 1
  - Introduction and References
  - The Scientific Method
  - Types of Medical Studies and how they are used/useful
  - The differences between evidence supporting a hypothesis and hypothesis generating information
- Break
- Lecture 2
  - Translating a hypothesis into an objective
  - Endpoints and how to pick a good one
  - The population of interest and sampling from it
- Lecture 3
  - Equipoise
  - Blinding
  - Randomization
- Lunch

Order and hopeful Timing - continued

- Lecture 4
  - Design of a simple randomized trial
- Stent vs no stent

Books

- Friedman LM, Furberg CD and DeMets DL: Fundamentals of Clinical Trials.
- Pocock SJ: Clinical Trials: A Practical Approach. Downloadable from the KI library.
- Design of Medical Studies course UW: http://www.emersonstatistics.com/courses/formal/b524_2011/index.asp

Full Credit to Professor Scott Emerson and Professor Thomas Fleming both of UW.
See handout for references

who I am

and what I don't know

1. I graduated from UW in 2011 with a PhD in Biostatistics
2. Previous job at NCI was to review biomarker aspects of cancer clinical trials
3. Served on DSMB boards, helped design trials, and write protocols
4. I am from the US, so I don't know the regulatory pathway in the EU, Yet!

Medical Studies

The goal of medical studies is to produce the evidence that can be used to

- Identify methods to diagnose disease
- Identify risk factors for disease
- Identify treatments for disease
- Identify methods for disease prognosis
- Identify strategies for prevention of disease
- Improve understanding of basic science

Is there a pathway to produce evidence?

The Scientific Method

"But in introducing me simultaneously to skepticism and to wonder, they taught me the two uneasily cohabiting modes of thought that are central to the scientific method."

- Carl Sagan, The Demon-Haunted World: Science as a Candle in the Dark, referring to his parents

Steps of the Scientific Method

Modified slightly for medical studies:

1. Form a hypothesis, **Write it down**.
2. Design and conduct an experiment to test/ provide evidence for that hypothesis.
3. Analyze the data from that experiment, using a pre-specified analysis plan, and draw a conclusion.
4. Present conclusions to scientific/medical community *ethically*
5. Determine if evidence convinces scientific/medical community
6. Update hypothesis and start over as needed.

Form a hypothesis

A pre-specified hypothesis is 100% necessary for evidence to support the hypothesis in all cases.

All machine learning, large cohort studies, observational studies with 100s of endpoints that attempt to conclude even that there is an underlying association between two things are flawed.

If you don't have a hypothesis before looking at the data collected or if your hypothesis changes after looking at the data you are still at step 1. **Some studies are run simply to generate hypotheses!**

Design a study

There are lots of different types of studies and there are many different steps/considerations when designing them. I will cover as much of this as I can over the rest of the day.

The important things to remember are:

- the pre-specification of the population, endpoints, analysis and protocol are all part of the design
- a well designed study is not one that gives you evidence to support your hypothesis, but one that gives sound evidence for or against your hypothesis.

Side Note: Disproof is Easier

Although the steps of the scientific method seem to be attempting to 'prove' the hypothesis, that is almost never the case.

In statistics we set up the null to be rejected. Providing proof of something is very hard, while providing evidence against it always being true is as simple as providing an example against it.

Therefore we provide evidence to support the hypothesis, by rejecting the contrapositive, we almost never prove the hypothesis in medical settings. (there is no medical gravity)

Data analysis

I am not going to cover data analysis here: Matteo has already covered much of it.

A well-designed simple trial should produce data you are able to analysis easily.

The type of analysis is part of the pre-specification needed. I will go into this is greater detail, but if you don't write down how you plan to analyze the data, prior to looking at it, this is as bad as changing your hypothesis.

Presentations of Conclusions

I am not going to try to teach you how to write a paper, I just want you to ask yourself:

- What is the ultimate goal of my research? - improve human health, uncover scientific truth....
- Are my conclusions statistically and scientifically valid for this trial?
- Is there previous evidence that support my conclusions, what is the overall weight of evidence for my conclusions?
- Could my conclusions although valid cause harm?
- If there is potential harm, is there a way to mitigate it?

Ethics of presentation

Who have you convinced

Is there still clinical equipoise?

- if there is no longer clinical equipoise, you need to modify your hypothesis and trial design or
- you have the needed evidence to convince the desired community

I will talk in more detail about clinical equipoise later today. Personal equipoise and clinical equipoise are different!

Update the hypothesis and start over

You do not find evidence to support your original hypothesis:

- a secondary or exploratory analysis may generate a new hypothesis
- need to redesign, retest new hypothesis in a new study.

You find evidence to support your original hypothesis, but people are not completely convinced:

- You need to run another trial to generate more evidence, for the same hypothesis
- The amount of evidence needed (to change clinical practice, get a new drug approved, ...) depends on many things

Anecdotal Observational Studies

- Case report
- Case series
- Unsupervised Machine learning
- ‘Data mining’

Designed observational study-1

- Case - Control
  - Sample diseased and non-diseased
  - Examine rates of exposures
- Why are these used
  - Efficient for rare diseases
  - Can look at multiple risk factors
- Limitations: cannot infer cause and effect
  - Correlations
  - Associations

Designed observational study-2

- Cohort Study
  - Sample exposed and non-exposed
  - Examine rates of disease
- Why are these used
  - Efficient for common diseases
  - Can look at multiple diseases
  - Can provide data from future retrospective trials
- Limitations : cannot infer cause and effect
  - Correlations
  - Associations

Designed interventional study-1

- Clinical trials 1 armed not randomized
  - Assign subjects to a treatment
  - Examine outcomes
- Why are these used
  - Fast
  - Allow you to put only a small number of subjects at risk
- Limitations: cannot infer cause and effect
  - gain information on extremely strong associations, maybe
  - make sure intervention isn't 100% fatal

Designed interventional study-2

- Clinical trials 2 or more armed randomized
  - Assign subjects to a treatment
  - Examine outcomes
- Why are these used
  - allow causal inference
  - gives clear answers
  - Can provide data for future retrospective trials
- Limitations: can be difficult to run
  - allow causal inference at the group level
  - still have to be careful what causes what

Experimentation in human volunteers - Scott Emerson UW

- Investigation of a new treatment or preventive agent
  - **Dose Finding**: What is the highest dose that can be used without causing toxicity?-Phase 1
  - **Safety**: Do adverse effects outweigh any benefit? - Phase I
  - **Activity**: Dose treatment cause activity in any known or suspected pathway of effect? -Phase II
  - **Efficacy**: Can treatment beneficially alter disease? - Phase III
  - **Effectiveness**: Would adoption of the treatment help population's health? - Phase III/IV
- Investigation of existing treatments
  - **Relative benefits**: Is one treatment clearly superior for the clinical endpoint? - Phase III/Phase IV
  - **Harm**: Should a therapy currently in use be removed? - Phase IV
- Investigation of a new treatment against Existing treatments
  - **Relative benefits**: Is new treatment clearly superior for the clinical endpoint? - Phase III
  - **Relative benefits**: Is the new treatment only marginally less effective than existing treatment but is easier to use, safer, has less side effects...etc.? - Phase III non-inferiority

Time Order for drug development

1. Anecdotal Observation
2. Designed case-control or cohort studies - background information
3. Pre-clinical experiments - Laboratory, animal studies of mechanisms, toxicology
4. Dose finding and safety studies - Phase I
5. Activity studies - Phase II
6. Efficacy studies - Phase III
7. Effectiveness studies - Phase III

Phase IV for population outcomes and long term monitoring.

Time Order for diagnostic testing

1. Anecdotal Observation
2. Designed case-control or cohort studies - developing the test
3. Randomized trials (Phase II/III) and Validation trials - testing accuracy

Phase IV and population and long term monitoring.

Phase III Efficacy

Definition of efficacy can vary widely according to choice of endpoint and magnitude of impact.

Does the treatment have sufficiently large effect on a clinically relevant endpoint under ideal conditions?

Does treatment have a sufficiently large effect on a clinically relevant endpoint in some subpopulation of the target population?

Phase III/IV Effectiveness

A treatment is effective if its introduction improves health in the target population.

- Need to compare safety and efficacy and the use of the treatment
  - Noncompliance
  - Off-label use
- Moving target that requires monitoring after an intervention is approved

Effectiveness vs Efficacy

A treatment can be 100% efficacious and be ineffective!

- most Phase III clinical trials are looking for efficacy
  - treatment only taken as directed and with good compliance.
  - treatment only given to subjects that meet the strict criteria.
  - treatment is compared to placebo or medically recognized standard of care.
- Effectivness
  - treatment is given as it would be in the clinic
  - treatment is given to anyone that needs it as determined by MD and themselves
  - treatment is compared to whatever else people are doing, which often includes off-label uses of other drugs

Evidence Supporting a Hypothesis

All for a pre-specified hypothesis by weight of evidence:

- The results from a group of well designed and run double-blinded randomized clinical trial
- The results from a well designed and run double-blinded randomized clinical trial
- The results from a well designed and well run randomized clinical trial
- The results from a well designed and well run prospective observational trial
- The results from a well designed and well run retrospective observational trial
- The results from a 1 armed interventional trial against historical controls
- The results from a 1 armed interventional trial with no historical controls
- The results of a case only observational study comparing to historical non-cases or the general population

Results that do NOT Support a Hypothesis

Any of the above for a result not about the pre-specified hypotheses

- Dimension reduction of high-dimensional data (data mining)
- Survey analysis without a directed hypothesis
- Registry studies without a directed hypothesis
- Random observation of a correlation of two things over time, or in general, that make no sense
- Any time you check everything and stop when you get a p-value < 0.05 (or less than any number)

Hypothesis Generation

The above list is great for generating hypothesis!

Except the last two, the last two are not good for anything other than muddying scientific knowledge and causing harm

...sometimes they are funny ...Jellybeans!
https://imgs.xkcd.com/comics/significant.png

Easy Example

More boys than girls - Thomas Fleming UW Biostatistics.

Harder Example

You spend 20 Million SEK testing a new drug for weight loss, Phase III Trial.
You find that there is no evidence to support weight loss is increased overall.
However, you do find

- that weight loss is increased in subjects aged ≤ 25 years with BMIs ≥ 31, p-value < 0.05.
- and that the drug dramatically reduces self reported sleeplessness, p-value< 0.001.[4]

- When would these conclusions be valid evidence of a causal relationship?
- When are these only hypothesis generating?
- When are these even questionable as hypothesis generating ideas?

Hardest Example

You develop a new drug to reduce heart damage after heart attack.
You run a well designed, randomized, blinded, placebo controlled, well powered trial and find that the treatment arm does indeed have a significant reduction in heart damage. Great! is this proof of the drug causing it....well yes, but not 100% how you think.
This is solid evidence that

- Randomizing subjects to treatment decreased heart damage
- Taking the drug is in the pathway of decreasing heart damage, somehow

What if the drug causes almost constant, but mild, headaches? What if people regularly treat these headaches with acetylsalicylic acid, causing a reduction in heart damage.[5]