INTRODUCTION TO CLINICAL RESEARCH

Scientific Concepts for Clinical Research

Karen Bandeen-Roche, Ph.D.

July 15, 2013

Acknowledgements

- Scott Zeger
- Marie Diener-West
- ICTR Leadership / Team

Section 1: The Science of Clinical Investigation

1. Platonic model: science as the search for "truth"
2. Scientific method: roles of evidence and belief
3. "Cause" – a counter-factual perspective
4. Comparing like to like
   i. Randomization
   ii. Stratification
   iii. Statistical adjustment

What Is Science?

Search for truth

Search for beauty

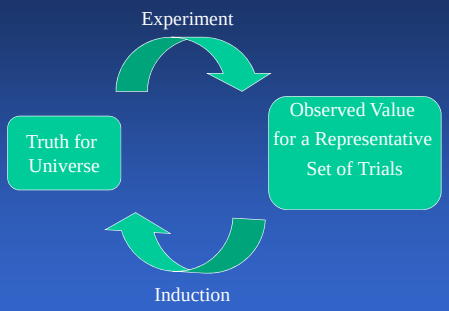
Ode on a Grecian Urn; John Keats (1795-1821)

When old age shall this generation waste,
Thou shalt remain, in midst of other woe
Than ours, a friend to man, to whom thou say'st,
"Beauty is truth, truth beauty,—that is all
Ye know on earth, and all ye need to know.

Scientific Method

- Competing hypotheses: H0, H1, H2, …
- Design an experiment to generate data
- Data support / falsify some hypotheses more than others

Search for Truth



Clinical Investigation

A *scientific* investigation that involves *patients*

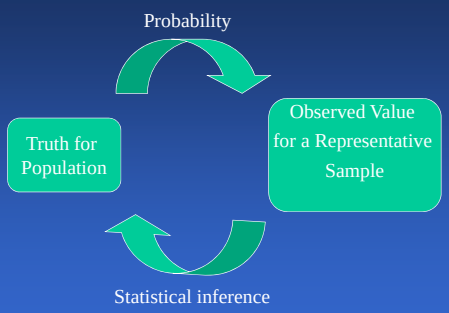
Scientific research where a clinician and patient are in the same room at least once

Key elements: Variability, uncertainty, prior beliefs

A thought example

- H1: Vitamin D supplementation delays the onset of frailty among pre-frail women
- H0: Vitamin D supplementation does not delay the onset of frailty among pre-frail women
- Experiment
  - Select a sample of pre-frail women
  - Randomize half to Vitamin D, half to placebo
  - Follow up to observe frailty onset

Search for Truth



Population vs. Sample

- KEY CONCEPT
- Population: What clinical experiments aim to say something about
  - Subject of hypotheses
- Sample: What clinical experiments *use* to support statements they make

Beauty: Scientific Method

- Competing hypotheses: H0, H1, H2, …
- Design an experiment to generate data
- Data support / falsify some hypotheses more than others

Coin Tossing Example

Truth we seek: how many heads on this coin?

Hypotheses: H0 – none; H1 – one; H2 - two

Design an experiment: flip the coin

Data As Evidence – One Toss Case

Probability of Experimental Result

	Numbers of Heads (Hypotheses)		
Result	0 (H0)	1 (H1)	2 (H2)
Heads (H)	0.0	0.5	1.0
Tails (T)	1.0	0.5	0.0

Measuring Evidence

- We toss coin once and get a head
- Probability of a head is twice as likely if the truth is that there are two heads on the coin than if one (Experimental result is twice as likely if H2 is true than if H1 is true)
- These data support H2 twice as much as H1

Real Experiment – Three Coin Tosses

- Prior beliefs about truth of universe?
  - 0 heads: 1 heads: 2 heads:
- Toss coin three independent times
- Results verified by adjudication committee

Probability of Experiment Result

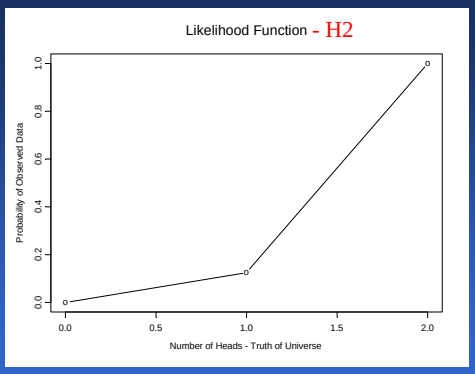
	Number of Heads on Coin		
Outcome	0	1	2
HHH			
HHT			
HTH			
HTT			
THH			
THT			
TTH			
TTT			

Probability of Experiment Result

	Number of Heads on Coin		
Outcome	0	1	2
HHH	0.0	.125	1.0
HHT	0.0	.125	0.0
HTH	0.0	.125	0.0
HTT	0.0	.125	0.0
THH	0.0	.125	0.0
THT	0.0	.125	0.0
TTH	0.0	.125	0.0
TTT	1.0	.125	0.0

Evidence

- Measured by the likelihood function
- Is always relative: supporting one hypothesis relative to another ("likelihood ratio")
- Is what science generates
- Is used to update prior beliefs



Interpreting Evidence

- Prior beliefs about truth of universe?
  - 0 heads: 1 heads: 2 heads:
- Likelihood of observed data
  - 0 heads: 0 1 heads: 0.125 2 heads: 1

Updating Prior Beliefs

Posterior Odds = Prior Odds x Likelihood Ratio

$$\frac{P(H2 \mid Data)}{P(H1 \mid Data)} = \frac{P(H2)}{P(H1)} \times \frac{P(Data \mid H2)}{P(Data \mid H1)}$$

("Bayesian" statistics)

Clinical Investigations to Determine "Cause"

- Definition of Cause (OED):

  "Something that brings about an effect or result."

  Merriam-Webster Online Dictionary
  http://www.merriam-webster.com/dictionary/cause

Whether a "cause" produces the "effect"

- Three queries (*Pearl, 2000*)
  - Predictions
    - "Probabilistic causality" (*von Suppes, 1970*)
    - Is frailty delay probable among the treated?
  - Interventions / Experiments (*Bollen, 1989*)
    - Association, temporality, isolation
    - Does an attenuation in frailty onset follow treatment?
  - Counterfactual
    - Does one's frailty onset differ if treated vs. not?
    - *Neyman, 1923; Stalnaker, 1968; Lewis, 1973; Rubin, 1974; Robins 1986; Holland 1988*

Counterfactual Definition of "Causal Effect" of Treatment

The difference between a population characteristic having given the treatment to everyone and the same characteristic absent the treatment

"Counterfactual" because we can not observe the response for a person both with and without the treatment (at one time). Each patient is either treated or not

Can be a useful way to organize ones thinking about "truth" in some circumstances

Counterfactual Data Table

Person	Vit D	Y(0)	Y(1)	Y(1)-Y(0)
1	0	22	16	-6
2	0	18	17	-1
3	0	20	15	-5
4	1	20	18	-2
5	1	18	16	-2
6	1	22	14	-8
Average		20	16	-4

Here: Y = frailty "score" (higher=worse)

25

Actual Data Table

Person	Vit D	Y(0)	Y(1)	Y(1)-Y(0)
1	0	22	?	?
2	0	18	?	?
3	0	20	?	?
4	1	?	18	?
5	1	?	16	?
6	1	?	14	?
Average		20	16	-4

26

Goal of Statistical "Causal" Inference

- "Fill-in" missing information in the counterfactual data table
- Use data for persons receiving the other treatment to fill-in a persons missing outcome
- Inherent assumption that the other persons are similar except for the treatment
- *Compare like-to-like*

Comparing Like-to-Like

Randomize treatment to persons

Stratify person into groups that are similar; make causal inference within groups and then pool results

Use a statistical adjustment to attain same end (regression analysis – more later)

Randomization

- We can *expect* the groups to be exchangeable with respect to measured and unmeasured variables
- Not necessarily similar in small studies
- Randomization is "successful" if you use a proper procedure, not if the data are apparently balanced on measured variables
- As a clinical investigator, always out-source the randomization

Stratification

- Used in randomization and/or analysis
- In analysis:
  - Divide sample into subsets of "similar" people
    - only similar for observed variables
  - Estimate treatment effects separately within each stratum
  - If treatment effect similar across strata ("no effect modification"), pool results

Main Points Once Again

A clinical investigation is a search for truth – how a treatment affects population, not only your sample.

Evidence is measured by the relative likelihood of the data under different hypotheses (a beautiful idea); beware prior opinions

"Cause" – a comparison of response with and without treatment for each person; inference involves filling in the missing boxes in the counterfactual data table

Compare like to like: randomization rules; stratification; statistical adjustment if necessary