Section 1: The Science of Clinical Investigation

1. Platonic model: science as the search for “truth”
2. Scientific method: role of evidence
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.

Search for Truth

Definition of Clinical Investigation

A scientific investigation that involves patients

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

- Competing hypotheses: H0, H1, H2, …
- Design an experiment to generate data
- Data support 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

<table>
<thead>
<tr>
<th>Probability of Experimental Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers of Heads (Hypotheses)</td>
</tr>
<tr>
<td>Result</td>
</tr>
<tr>
<td>Heads (H)</td>
</tr>
<tr>
<td>Tails (T)</td>
</tr>
</tbody>
</table>
Measuring Evidence

- We toss coin once and get a tail
- Probability of a tail is twice as likely if the truth is that there are two tails (no heads) on the coin than if one
  (Experimental result is twice as likely if H0 is true than in H1 is true)
- These data support H0 twice as much as H1

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 in 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**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHH</td>
<td>0.0</td>
<td>.125</td>
<td>1.0</td>
</tr>
<tr>
<td>HHT</td>
<td>0.0</td>
<td>.125</td>
<td>0.0</td>
</tr>
<tr>
<td>HTH</td>
<td>0.0</td>
<td>.125</td>
<td>0.0</td>
</tr>
<tr>
<td>HTT</td>
<td>0.0</td>
<td>.125</td>
<td>0.0</td>
</tr>
<tr>
<td>THH</td>
<td>0.0</td>
<td>.125</td>
<td>0.0</td>
</tr>
<tr>
<td>THT</td>
<td>0.0</td>
<td>.125</td>
<td>0.0</td>
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<tr>
<td>TTH</td>
<td>0.0</td>
<td>.125</td>
<td>0.0</td>
</tr>
<tr>
<td>TTT</td>
<td>1.0</td>
<td>.125</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Interpreting Evidence**

- Prior beliefs about truth of universe?
  - 0 heads: .2  
  - 1 heads: .8  
  - 2 heads: 0

- Likelihood of observed data
  - 0 heads  
  - 1 heads  
  - 2 heads:
Updating Prior Beliefs

Posterior Odds = Prior Odds x Likelihood Ratio

\[
P(H2 | Data) = \frac{P(H2)}{P(H1)} \times \frac{P(Data | H2)}{P(Data | H1)}
\]

Interpreting Evidence

- Prior beliefs about truth of universe?
  - 0 heads: 1 heads: 2 heads:

- Likelihood of Observed Data
  - 0 heads: 1 heads: 2 heads:

- Posterior beliefs about truth of universe?
  - 0 heads: 1 heads: 2 heads:
Clinical investigations to determine “cause”

- Definition of Cause (OED):
  
  “That which produces an effect; that which gives rise to any action, phenomenon, or condition.”

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 cannot 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 one’s thinking about “truth” in some circumstances.

Counterfactual data table

<table>
<thead>
<tr>
<th>Person</th>
<th>Drug</th>
<th>$Y(0)$</th>
<th>$Y(1)$</th>
<th>$Y(1) - Y(0)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>22</td>
<td>16</td>
<td>-6</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>18</td>
<td>17</td>
<td>-1</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>20</td>
<td>15</td>
<td>-5</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>20</td>
<td>18</td>
<td>-2</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>18</td>
<td>16</td>
<td>-2</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>22</td>
<td>14</td>
<td>-8</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>20</td>
<td>16</td>
<td>-4</td>
</tr>
</tbody>
</table>
### Actual Data Table

<table>
<thead>
<tr>
<th>Person</th>
<th>Drug</th>
<th>Y(0)</th>
<th>Y(1)</th>
<th>Y(1)-Y(0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>22</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>18</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>20</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>?</td>
<td>18</td>
<td>?</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>?</td>
<td>16</td>
<td>?</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>?</td>
<td>14</td>
<td>?</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>20</td>
<td>16</td>
<td>-4</td>
</tr>
</tbody>
</table>

### 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 person's 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 similar with respect to measured and unmeasured variables
- Not necessarily similar in small studies
- Randomization are “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 effects population, not only your sample.

Evidence is measured by the relative likelihood of the data under different hypotheses; 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