What is a “Win” in a two-arm trial with counterfactual placebo?

Jim Hughes
Dept. of Biostatistics
University of Washington

(in collaboration with Fei Gao, Dave Glidden, Deborah Donnell)
Study design

Screen N

HIV positive N+

Recency test N+ test

HIV negative N-

Active control N-,1

Experimental N-,2

\[ p \quad q \quad r \quad \text{randomize} \]
What is required for approval?

I. Experimental is superior to Placebo AND Experimental has prevention efficacy comparable to the Active control

II. Experimental is superior to Placebo OR Experimental has prevention efficacy comparable to the Active control

III. Experimental is superior to Placebo AND the Active control is superior to Placebo

IV. Other?
E is superior to P AND E has comparable efficacy as A

P = Placebo incidence (from recency, counterfactual, other)
A = Active Control Incidence
E = Experimental Drug Incidence

I) Superiority:

\[ H_0^1: \frac{E}{P} = m_S \]
\[ H_a^1: \frac{E}{P} < m_S \]

II) Similar prevention efficacy

\[ H_0^2: \frac{E}{P} - \frac{A}{P} = m_C \]
\[ H_a^2: \frac{E}{P} - \frac{A}{P} < m_C \]

**Win:** Reject \( H_0^1 \) and \( H_0^2 \)
Example

• Suppose we want to show the new drug is at least 50% effective \((E/P=0.5)\)
• Also, we expect the current SOC is 60% effective \((A/P = 0.4)\)

I) Superiority:

\[
\begin{align*}
\text{H}_0^1: & \quad \frac{E}{P} = 0.5 \\
\text{H}_a^1: & \quad \frac{E}{P} < 0.5
\end{align*}
\]

II) Similar prevention efficacy:

\[
\begin{align*}
\text{H}_0^2: & \quad \frac{E}{P} - \frac{A}{P} = 0.1 \\
\text{H}_a^2: & \quad \frac{E}{P} - \frac{A}{P} < 0.1
\end{align*}
\]
Testing H1 and H2

**Testing one hypothesis**
- Form a Z-statistic
- Reject Ho if $Z < q$
- Pick $q$ so $P(Z < q \mid \text{Ho true}) = \alpha$
  - For $\alpha = 0.025$, $q = -1.96$

**Testing two hypotheses**
- Form a Z-statistic for each hypothesis
- Reject Ho if $Z_s < q_s$ and $Z_C < q_C$
- Pick $q$ so $P(Z_s < q_s, Z_C < q_C \mid \text{Ho true}) = \alpha$
  - For $\alpha = 0.025$, $q_s = q_C = -1.49$ (if P, A, E equally precise)
- Can allocate $\alpha$ equally or differently between the two hypotheses
Sample Size

The following design parameters must be specified for any given trial.

- **Expected placebo incidence rate**
- Recency test characteristics (FRR, MDRI, T, relative SE’s)
- Other design parameters (p, q, r, followup time)
- **Superiority and prevention efficacy margins under Ho - m_S, m_C**
- Desired power and effect sizes under Ha
- Overall $\alpha$ and/or allocation of $\alpha$ between $H^1$ and $H^2$
Sample size is the number of persons screened.
Assumptions: 90% of HIV negative individuals enroll on PrEP, 90% of HIV positive specimens yield valid recency testing results, two years of follow-up on PrEP, 7% RSE on the MDRI, 25% RSE on FRR, significance level 0.025 (one-sided) and 80% power.

<table>
<thead>
<tr>
<th>US MSM</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>3.42%/yr</td>
</tr>
<tr>
<td>Prevalence</td>
<td>14.5%</td>
</tr>
<tr>
<td>subtype</td>
<td>B</td>
</tr>
<tr>
<td>MDRI (days)</td>
<td>142</td>
</tr>
<tr>
<td>FRR</td>
<td>1.0%</td>
</tr>
<tr>
<td>Sample size – 1 arm</td>
<td>2,190</td>
</tr>
<tr>
<td>Sample size – 2 arm</td>
<td>2,608</td>
</tr>
</tbody>
</table>
Conclusions

• Two arm trial with counterfactual placebo and active control
  • ... requires testing two hypotheses
  • ... is appropriate for a new agent that is expected to be highly effective
  • ... is feasible in terms of sample size
• Can be used with other approaches to estimating counterfactual placebo incidence
• Need to be intentional about setting type I error rate and power for each (sub)hypothesis
Acknowledgments

• Overall support for the HIV Prevention Trials Network (HPTN) is provided by the National Institute of Allergy and Infectious Diseases (NIAID), Office of the Director (OD), National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), the National Institute of Mental Health (NIMH), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) under Award Numbers UM1AI068619-15 (HPTN Leadership and Operations Center), UM1AI068617-15 (HPTN Statistical and Data Management Center), and UM1AI068613-15 (HPTN Laboratory Center).

• The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.