Adaptive Non-Inferiority Margins: When Adherence is Not as Expected

Brett Hanscom, PhD
HPTN SDMC
Seattle, WA
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Introduction

• Non-inferiority design
  – Determine whether an experimental product is not meaningfully worse than an active-control therapy.

• Example: HPTN 083
  – Randomized trial of injectable Cabotegravir as long-acting PrEP
  – Active-control group: Oral TDF/FTC
Non-Inferiority Margin

• The non-inferiority margin is the numerical threshold beyond which a new product would be considered unacceptably worse.
• This is typically derived from the results of prior clinical trials, using meta analysis.
• Strong predictors of effectiveness, such as adherence, can make the margin more precise.
META-REGRESSION RESULTS

Relative Risk (RR) - Placebo vs. Active PrEP

Women
Men

Adherence

Adherence
META-REGRESSION RESULTS
META-REGRESSION RESULTS
PLANNED NON-INFERIORITY MARGIN – 60% ADHERENCE

Relative Risk relative to the Active Control (log scale)

- Experimental vs. Active-Control (Planned Trial)
- Planned Margin
- Active-Control Benefit (Prior Trials)

Relative Risk: 1.0, 1.23, 1.50
What happens if adherence is not as planned?

Effectiveness of TDF/FTC will not be as planned either, and the selected NI margin will be invalid.

We have a violation of the constancy assumption.

Type-I error and power may suffer.
OBSERVE 55% ADHERENCE – MARGIN IS TOO HIGH – INFLATED TYPE-I ERROR

Experimental vs. Active-Control (Planned Trial)

Correct Margin

Estimated Active-Control Benefit

Relative Risk relative to the Active Control (log scale)
OBSERVE 70% ADHERENCE – MARGIN IS TOO HIGH – LOW POWER

Experimental vs. Active-Control (Planned Trial)

Relative Risk relative to the Active Control (log scale)

Correct Margin

Observed Active-Control Benefit

1.0

1.37

1.89
## Type-I error and power, wrong margin

<table>
<thead>
<tr>
<th>Observed Adherence</th>
<th>Estimated TDF/FTC Benefit</th>
<th>NI Margin Preserving 50% Benefit</th>
<th>Type-I Error</th>
<th>Power**</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.50</td>
<td>1.17</td>
<td>1.08</td>
<td>0.13</td>
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<td>0.55</td>
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<td>1.15</td>
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<tr>
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<td><strong>1.23</strong></td>
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<td>0.70</td>
<td>1.89</td>
<td>1.37</td>
<td>0.004</td>
<td>0.71</td>
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</tbody>
</table>

* Planned level of adherence
** Assuming RR = 0.75
Proposal – Adaptive Margins

• Measure drug adherence in the active-control arm during/after the trial
• Re-compute the NI Margin based on the observed population values
• Apply this adapted margin to the final endpoint results
Adapted Null Hypothesis

- The adapted margin becomes the adapted null hypothesis
- In a superiority
  - $H_0: \text{RR} = 1.0$
- In a NI trial
  - $H_0: \text{RR} = \text{NI Margin}$
- In an adaptive margin NI trial
  - $H_0: \text{RR} = \text{“Preserve 50% of Benefit”}$
## Corrected Type-I Error

<table>
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<tr>
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* Planned level of adherence
ALTERNATIVE HYPOTHESIS UNDER A FIXED SAMPLE SIZE (N=172)

Relative Risk relative to the Active Control (log scale)

Planned Alt

Effect Size

Planned Margin

0.75  1.0  1.23
ALTERNATIVE HYPOTHESIS UNDER A FIXED SAMPLE SIZE (N=172)

Relative Risk relative to the Active Control (log scale)
New Alternative Hypothesis

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<th>Observed Adherence</th>
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<th>Alternative with 90% Power</th>
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* Planned level
Pre-specification

• The meta-regression model used for adapting the margin is based entirely on external trials.
• The adapted NI margin depends only on adherence observed in the active control arm, and not on the observed effect size.
• Procedures for measuring adherence, should be carefully pre-specified.
Cautions

- The meta-regression model is not perfect.
- Assessment of adherence is not perfect, and may not be identical to the way adherence was measured previously.
- These methods are in development and not yet approved by the FDA for HPTN 083.
Summary

• It will be increasingly common to see non-inferiority trials for HIV prevention
• Essential to consider adherence levels in the study population when planning and analyzing these trials
• Adaptive NI margins can be a helpful tool when adherence is not as planned and the constancy assumption fails
ACKNOWLEDGEMENTS

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Collaborators:
Deborah Donnell, Jim Hughes
HPTN SDMC / SCHARP
Brian Williamson
University of Washington