HPTN
HIV Prevention
Trials Network

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

Brett Hanscom, PhD
HPTN SDMC
Seattle, WA
4/11/2017

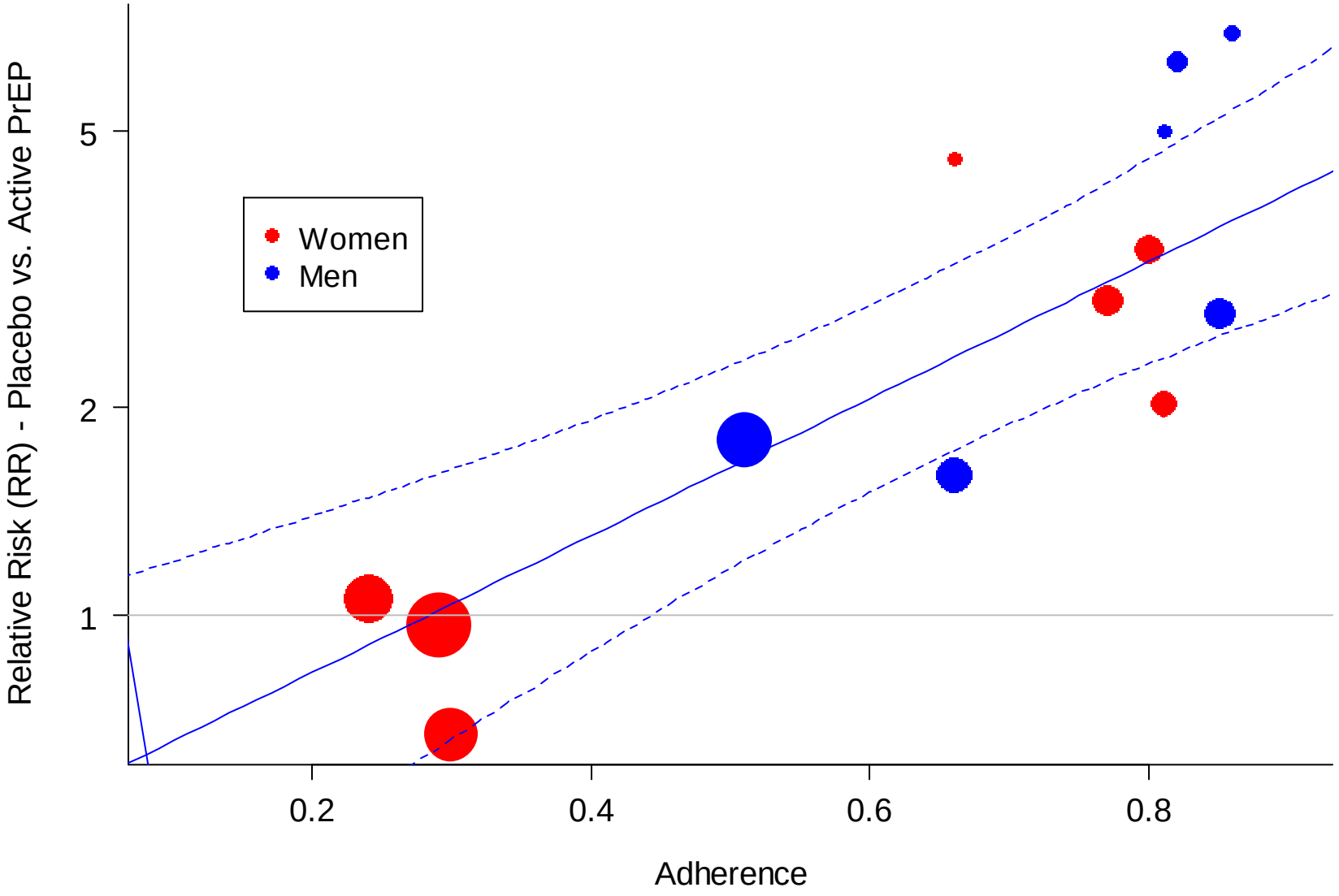
Introduction

- 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

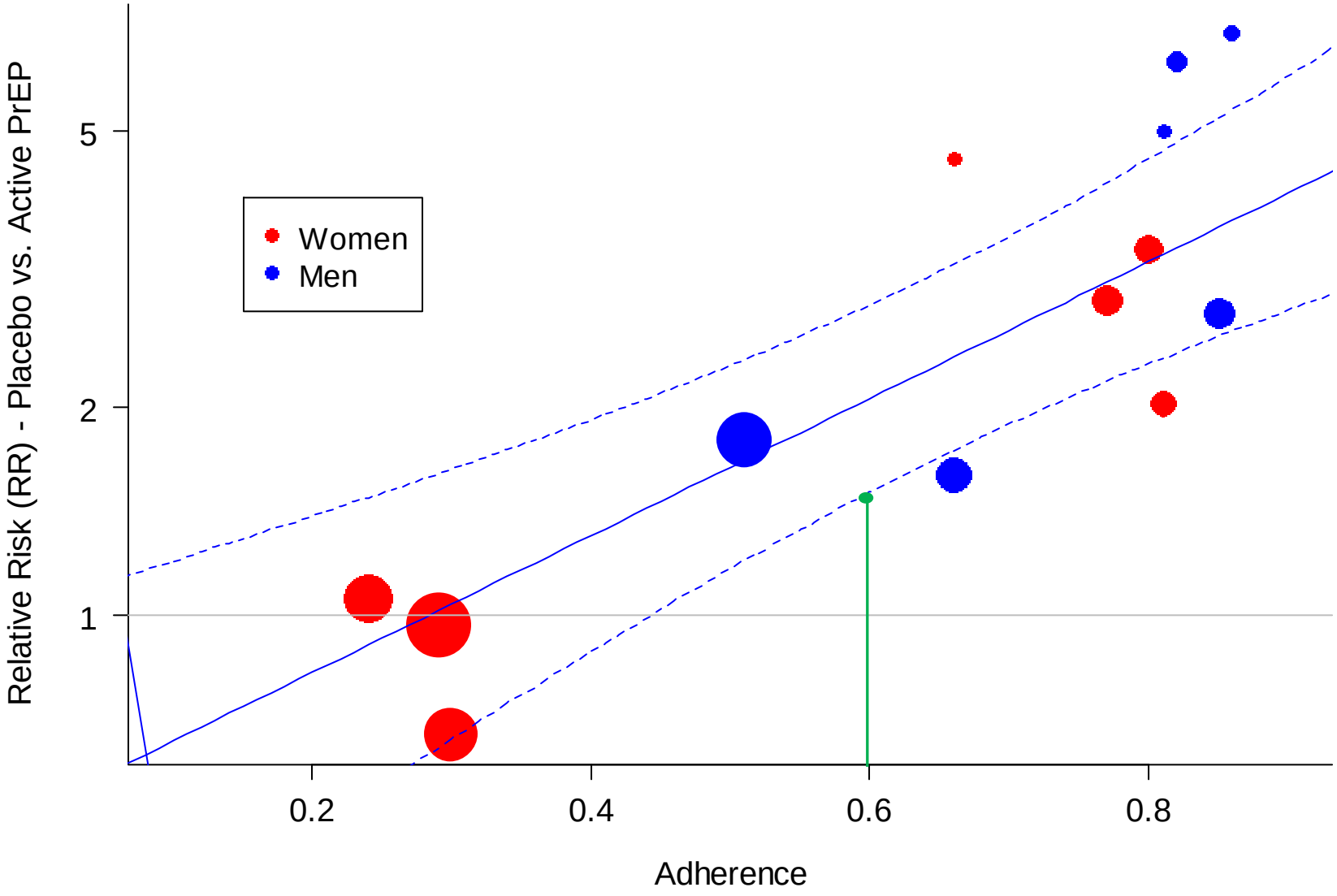
Non-Inferiority Margin

- 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.

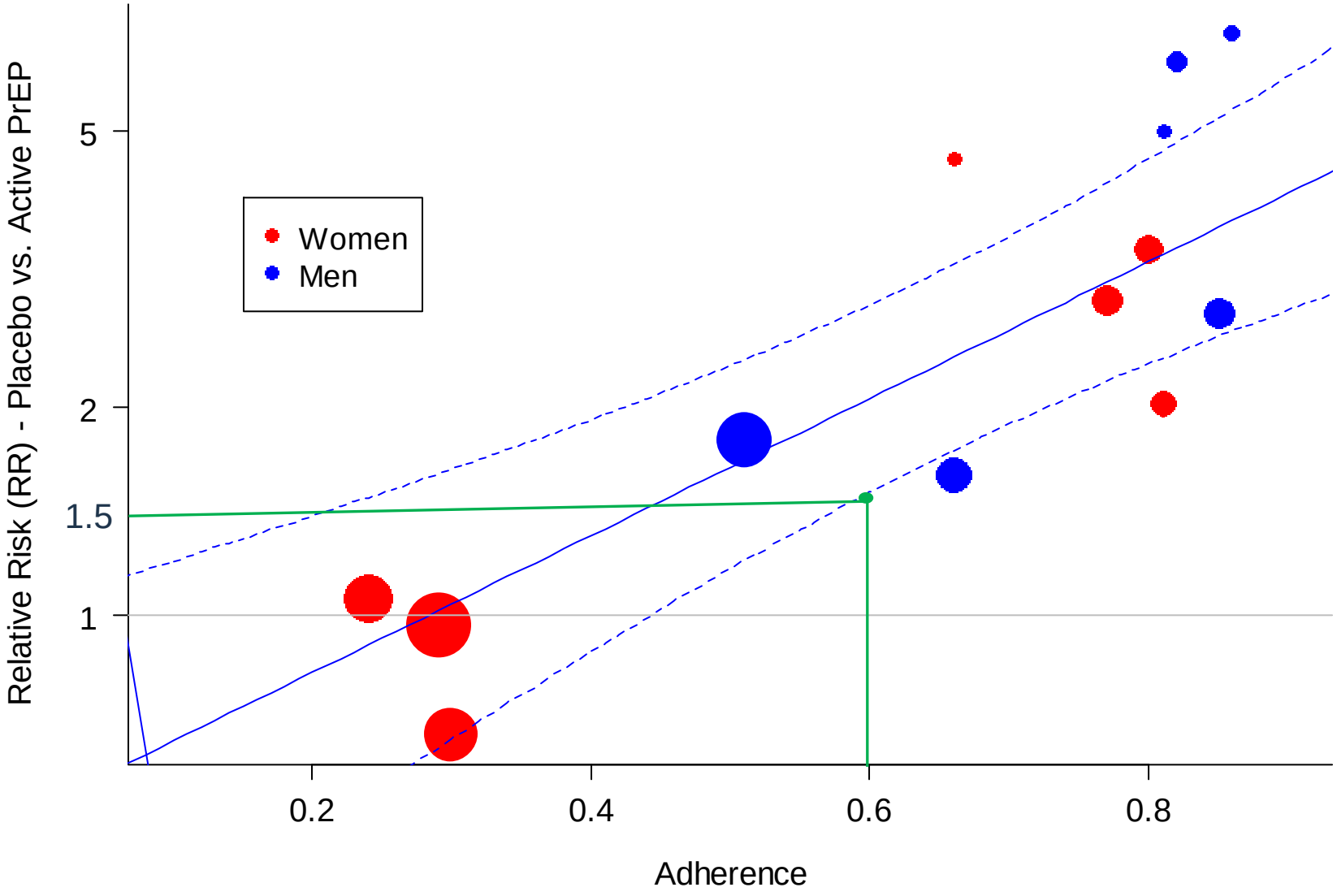
META-REGRESSION RESULTS



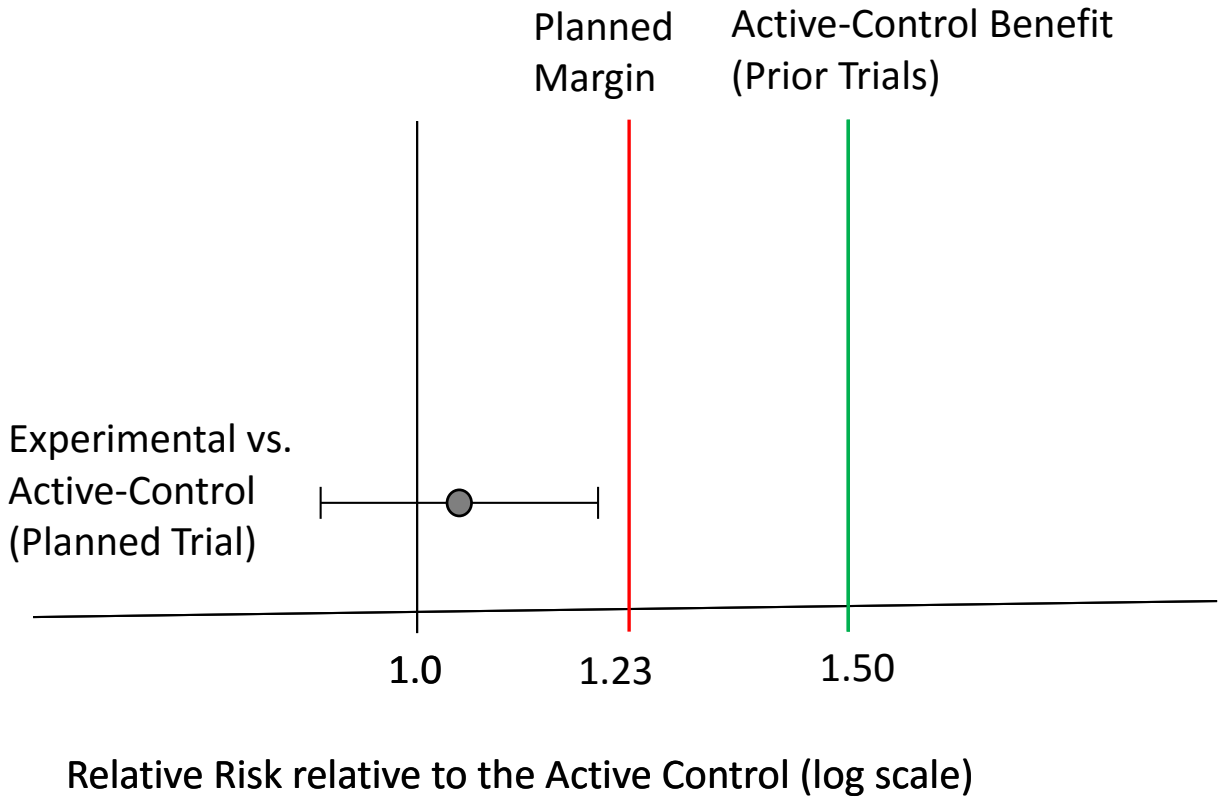
META-REGRESSION RESULTS



META-REGRESSION RESULTS



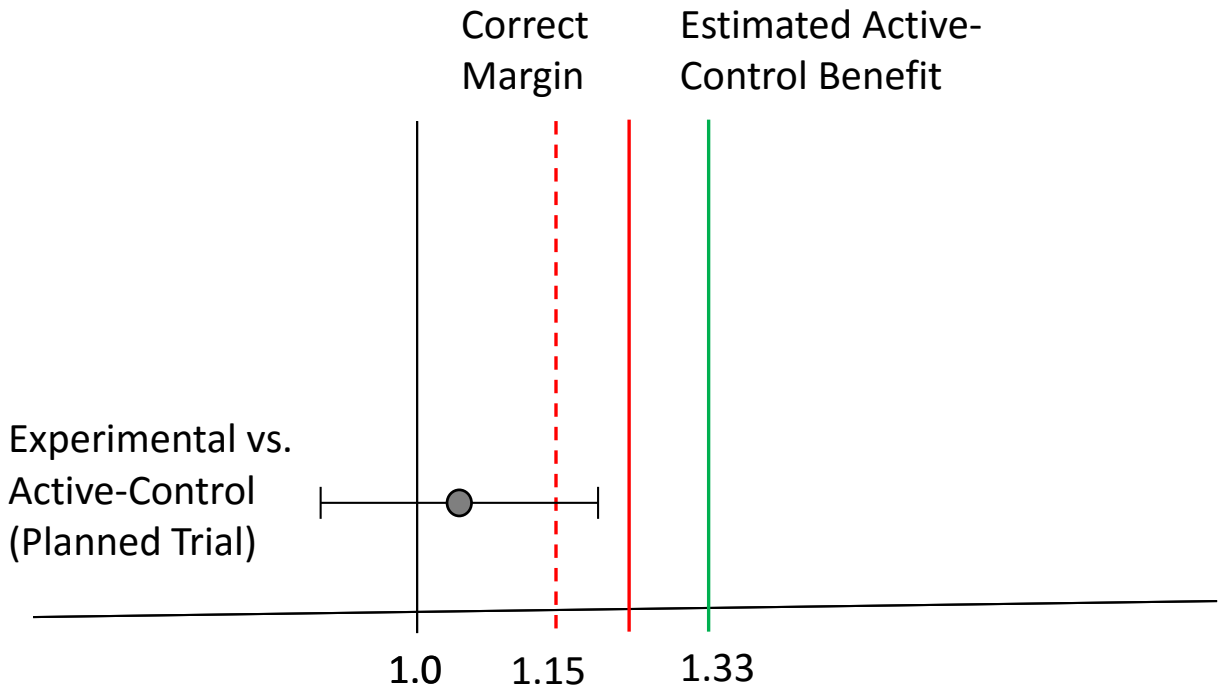
PLANNED NON-INFERIORITY MARGIN – 60% ADHERENCE



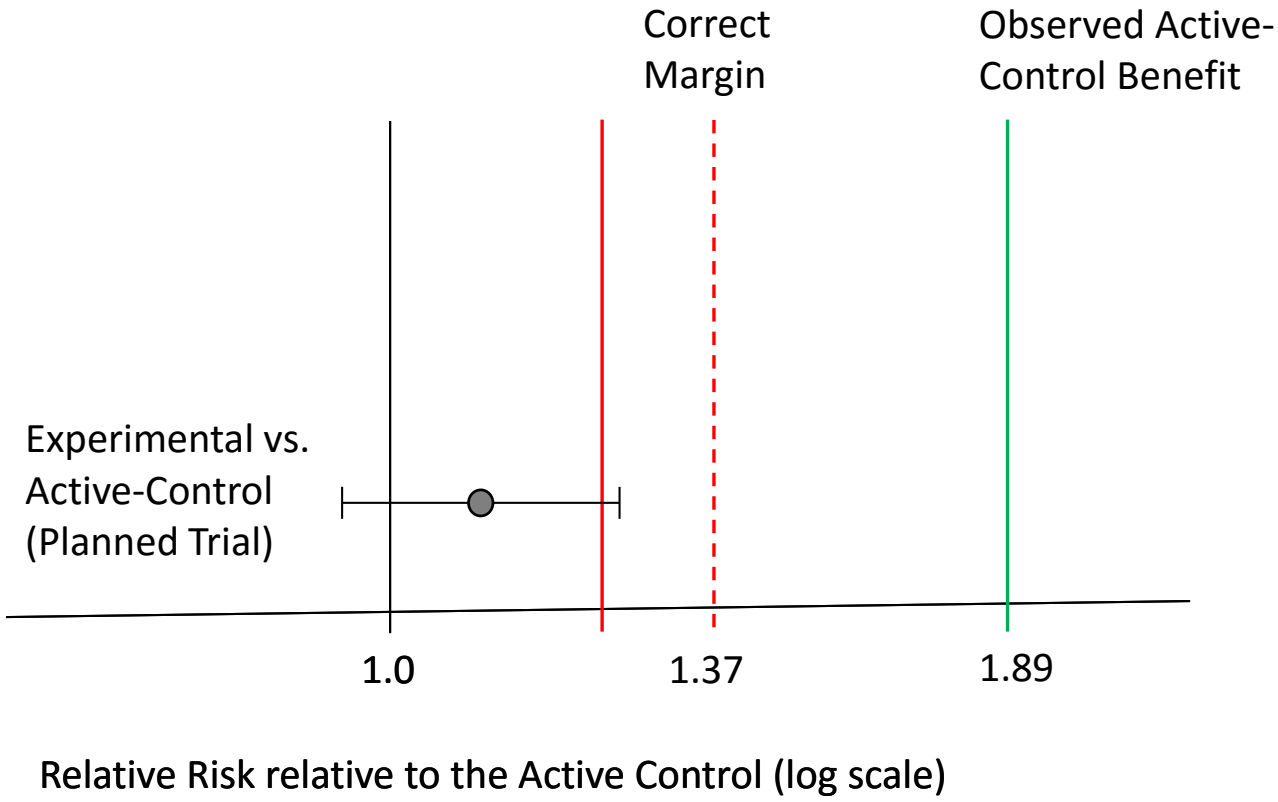
Constancy

- 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



OBSERVE 70% ADHERENCE – MARGIN IS TOO HIGH – LOW POWER



Type-I error and power, wrong margin

Observed Adherence	Estimated TDF/FTC Benefit	NI Margin Preserving 50% Benefit	Type-I Error	Power**
0.50	1.17	1.08	0.13	0.98
0.55	1.33	1.15	0.06	0.95
0.60*	**1.5**	**1.23**	**0.025**	**0.90**
0.65	1.69	1.30	0.01	0.82
0.70	1.89	1.37	0.004	0.71

* 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

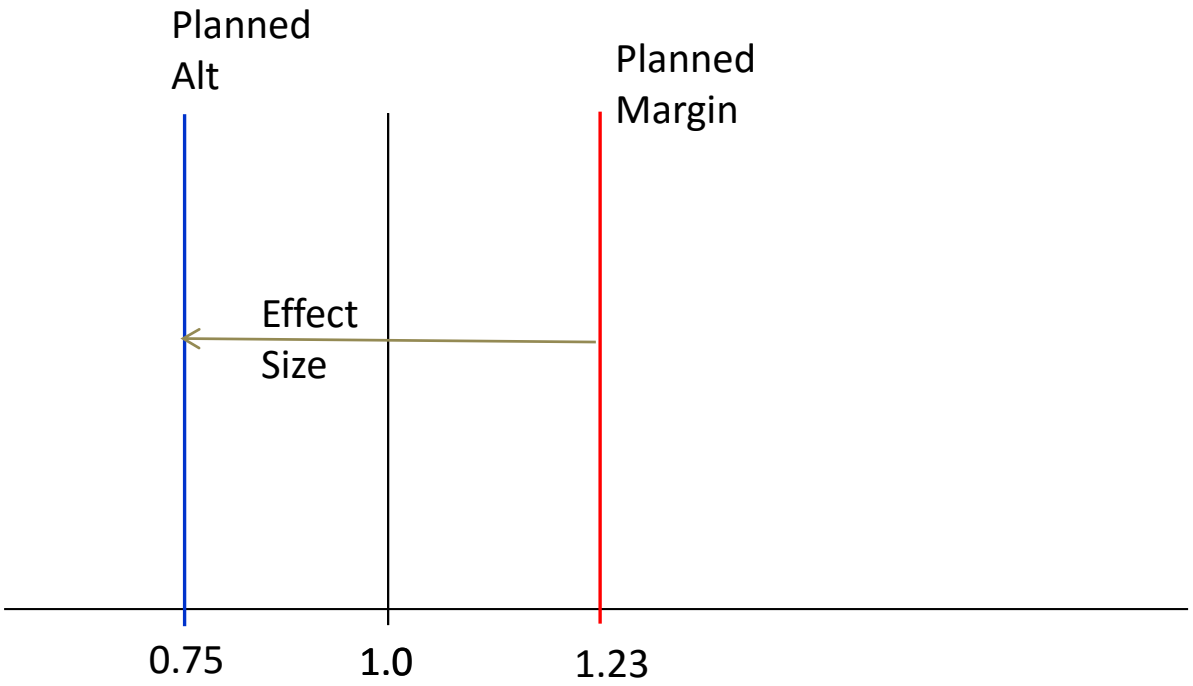
- The adapted margin becomes the adapted null hypothesis
- In a superiority
  - H_0: RR = 1.0
- In a NI trial
  - H_0: RR = NI Margin
- In an adaptive margin NI trial
  - H_0: RR = “Preserve 50% of Benefit”

Corrected Type-I Error

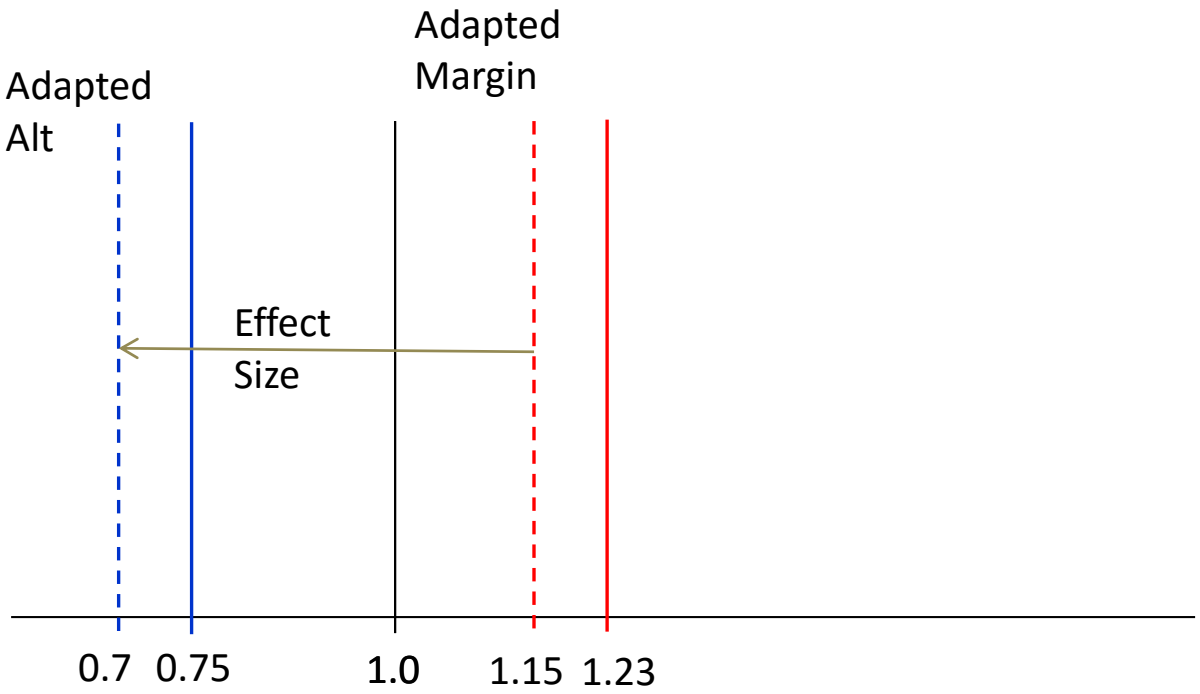
Observed Adherence	Estimated TDF/FTC Benefit	Adapted NI Margin	Type-I Error
0.50	1.17	1.08	0.025
0.55	1.33	1.15	0.025
0.60*	**1.50**	**1.23**	**0.025**
0.65	1.69	1.30	0.025
0.70	1.89	1.37	0.025

* Planned level of adherence

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



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



New Alternative Hypothesis

Observed Adherence	Estimated TDF/FTC Benefit	Adapted NI Margin	Type-I Error	Alternative with 90% Power
0.50	1.17	1.08	0.025	0.66
0.55	1.33	1.15	0.025	0.70
0.60*	**1.50**	**1.23**	**0.025**	**0.75**
0.65	1.69	1.30	0.025	0.79
0.70	1.89	1.37	0.025	0.83

* 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

HPTN
HIV Prevention
Trials Network

ACKNOWLEDGEMENTS

The HIV Prevention Trials Network is sponsored by the National Institute of Allergy and Infectious Diseases, the National Institute of Mental Health, and the National Institute on Drug Abuse, all components of the U.S. National Institutes of Health.

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