HPTN
HIV Prevention
Trials Network

Designing Non-Inferiority Trials when the Non-inferiority Margin Depends on Adherence – HPTN 083

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Introduction

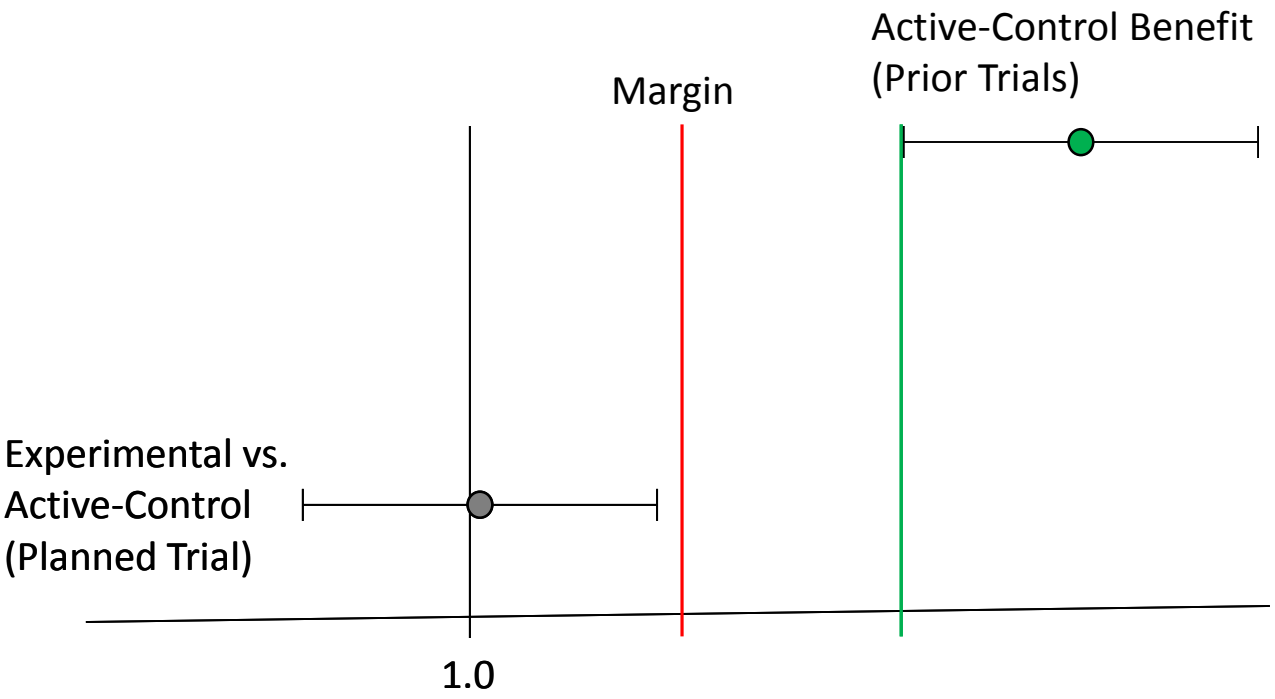
- HPTN 083
  - Randomized trial of injectable Cabotegravir as long-acting PrEP
  - Active-control group: Oral TDF/FTC
- Non-inferiority design
  - Determine whether the experimental product is not meaningfully worse than TDF/FTC

Non-Inferiority Margin

- We need to pre-specify what we mean by "not meaningfully worse"

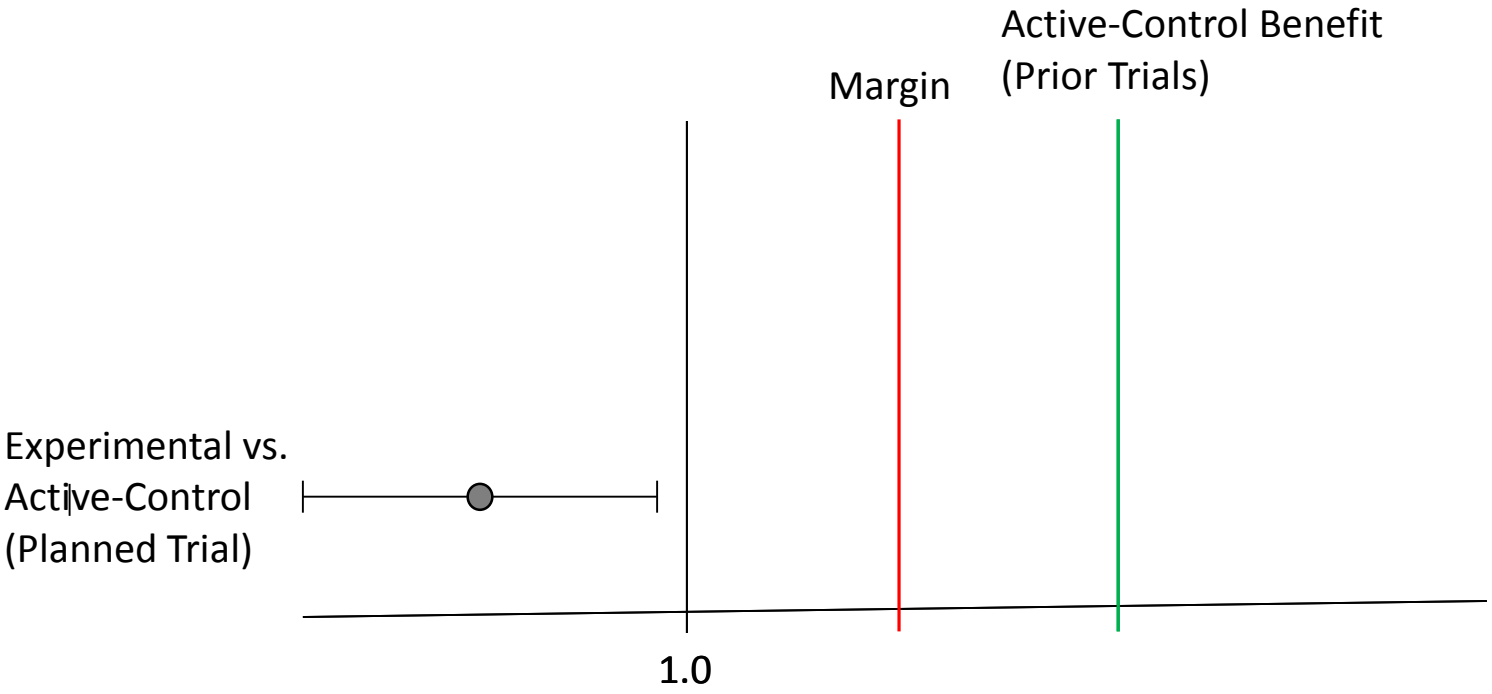
- The non-inferiority margin is the numerical threshold beyond which a new product would be considered unacceptably worse.

NON-INFERIORITY MARGIN



Relative Risk relative to the Active Control (log scale)

NON-INFERIORITY MARGIN



Requirements for an NI Trial

- It is critical that the active control have the same effect in the new trial as it did in prior trials

- The constancy assumption could be violated if adherence were higher or lower than in prior trials

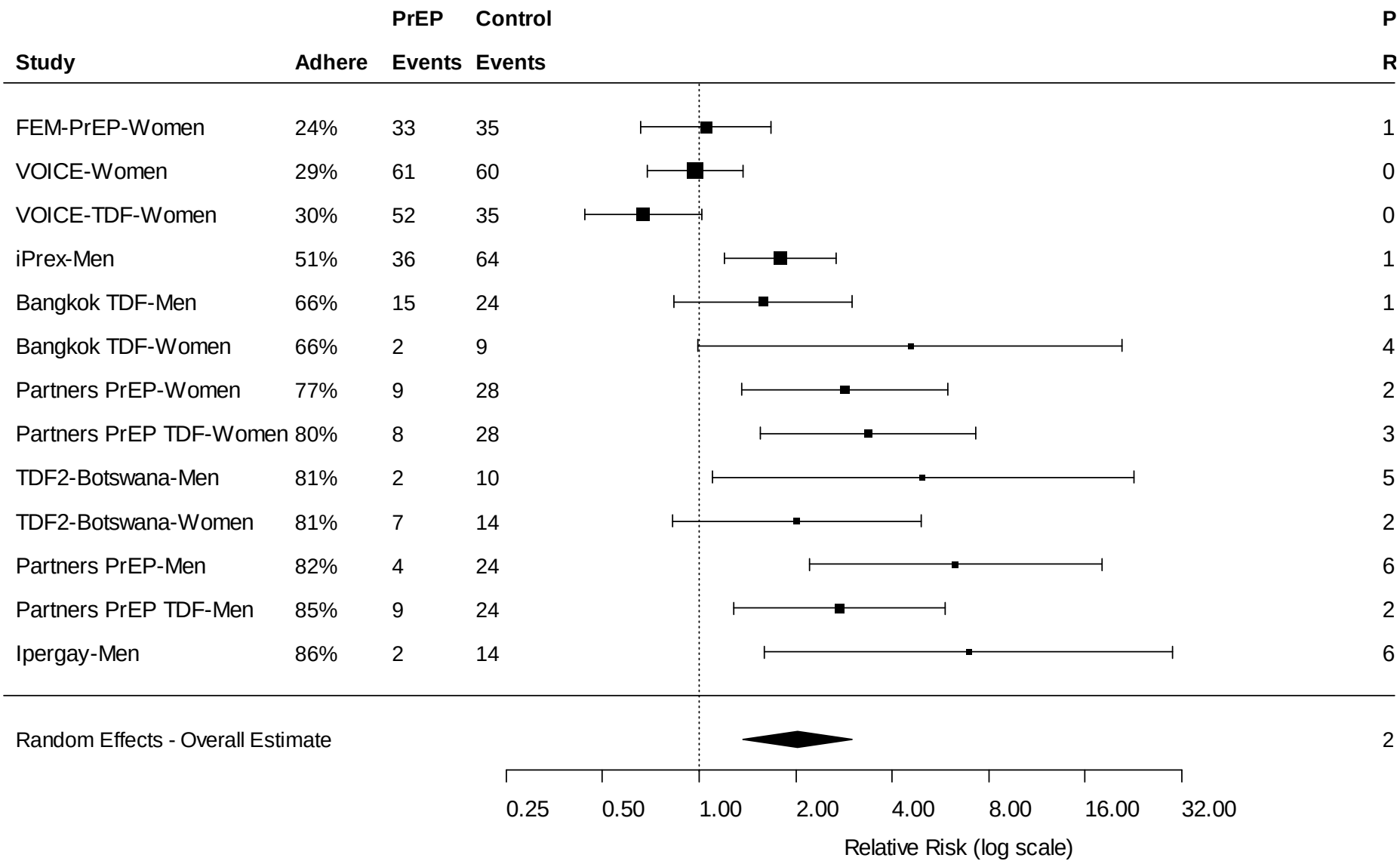
Goals

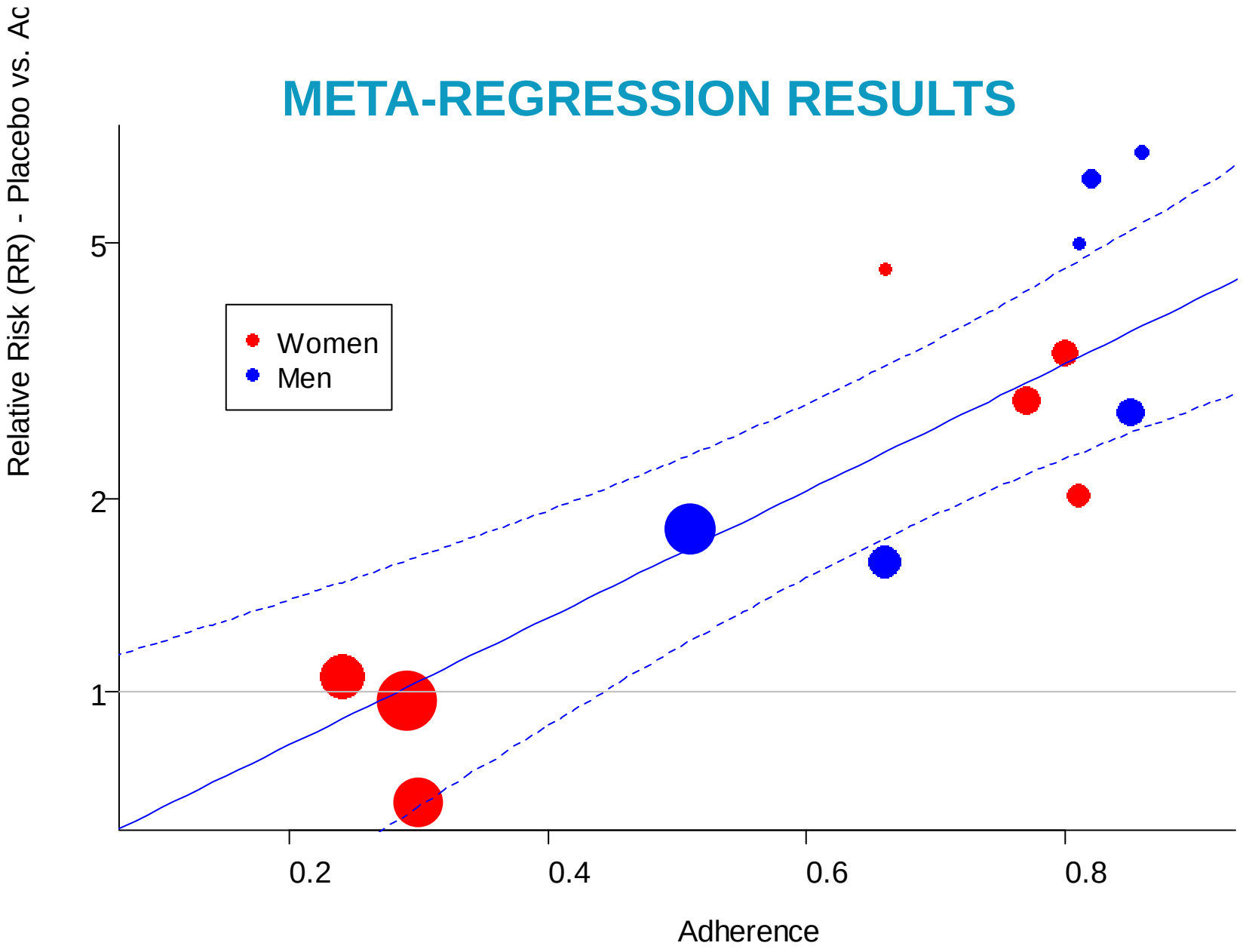
- Develop a method for computing an appropriate NI margin
- Incorporate results from all oral TDF or TDF/FTC PrEP trials
- Explicitly address the potential for non-constancy

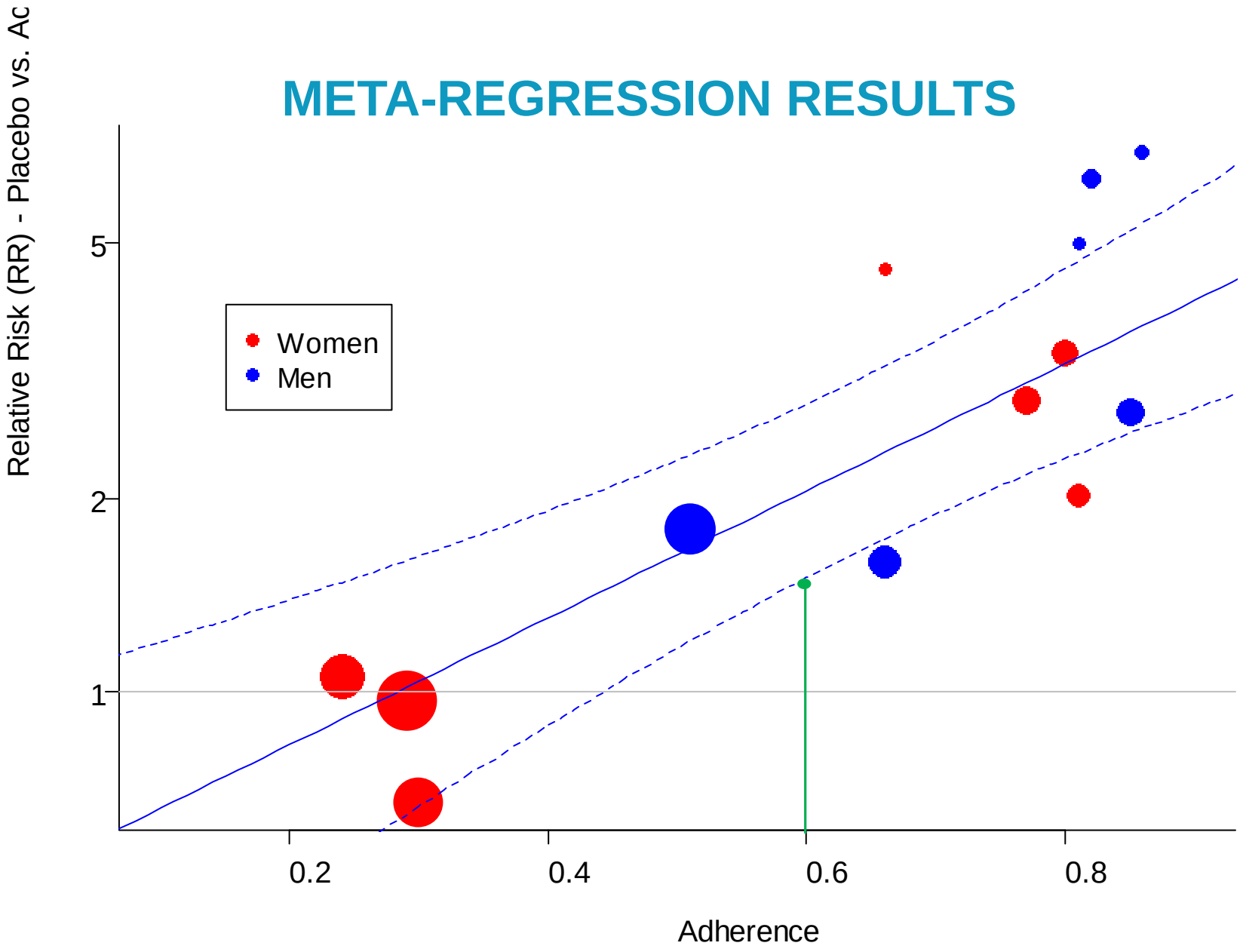
Proposed Method

- Meta-analysis regression
- Include a range of high-quality oral TDF(/FTC) trial results
- Incorporate measured adherence and sex
- Fit model
- Use anticipated adherence to compute a targeted NI margin

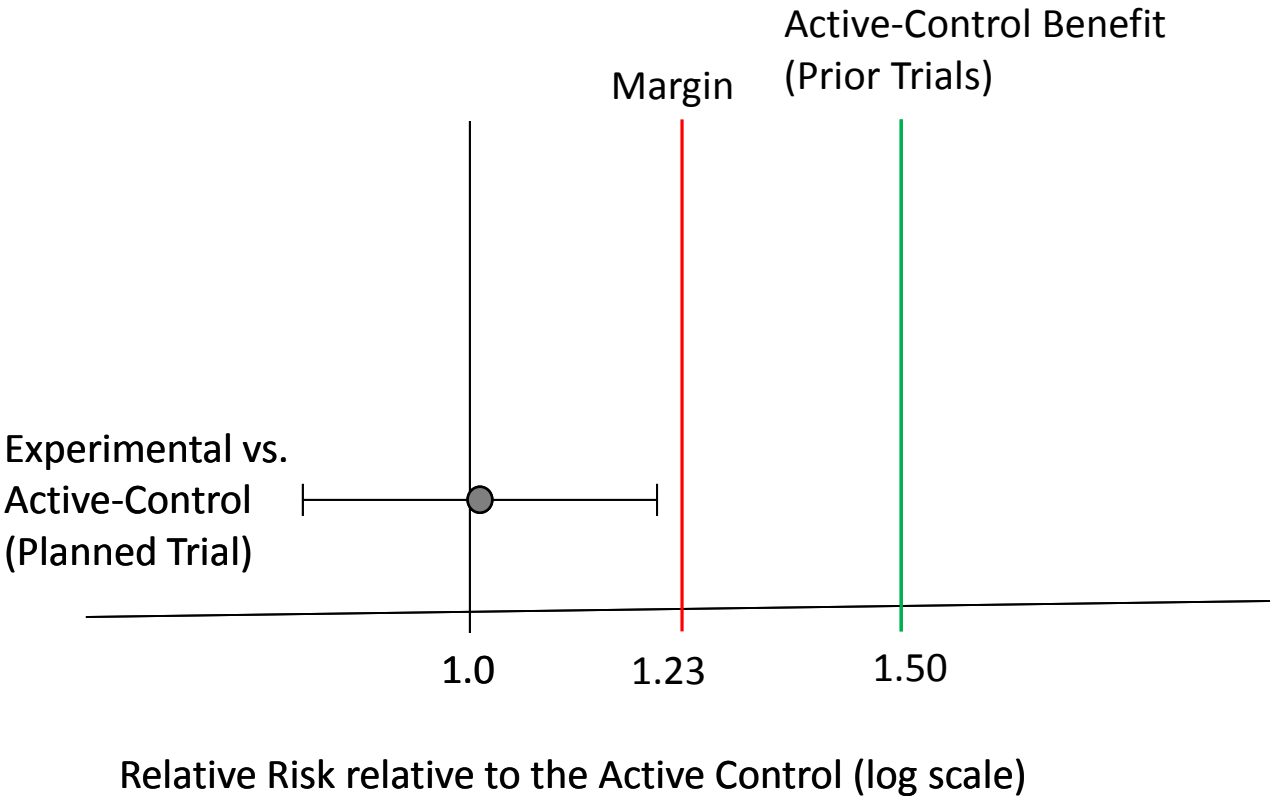
SIMPLE META ANALYSIS

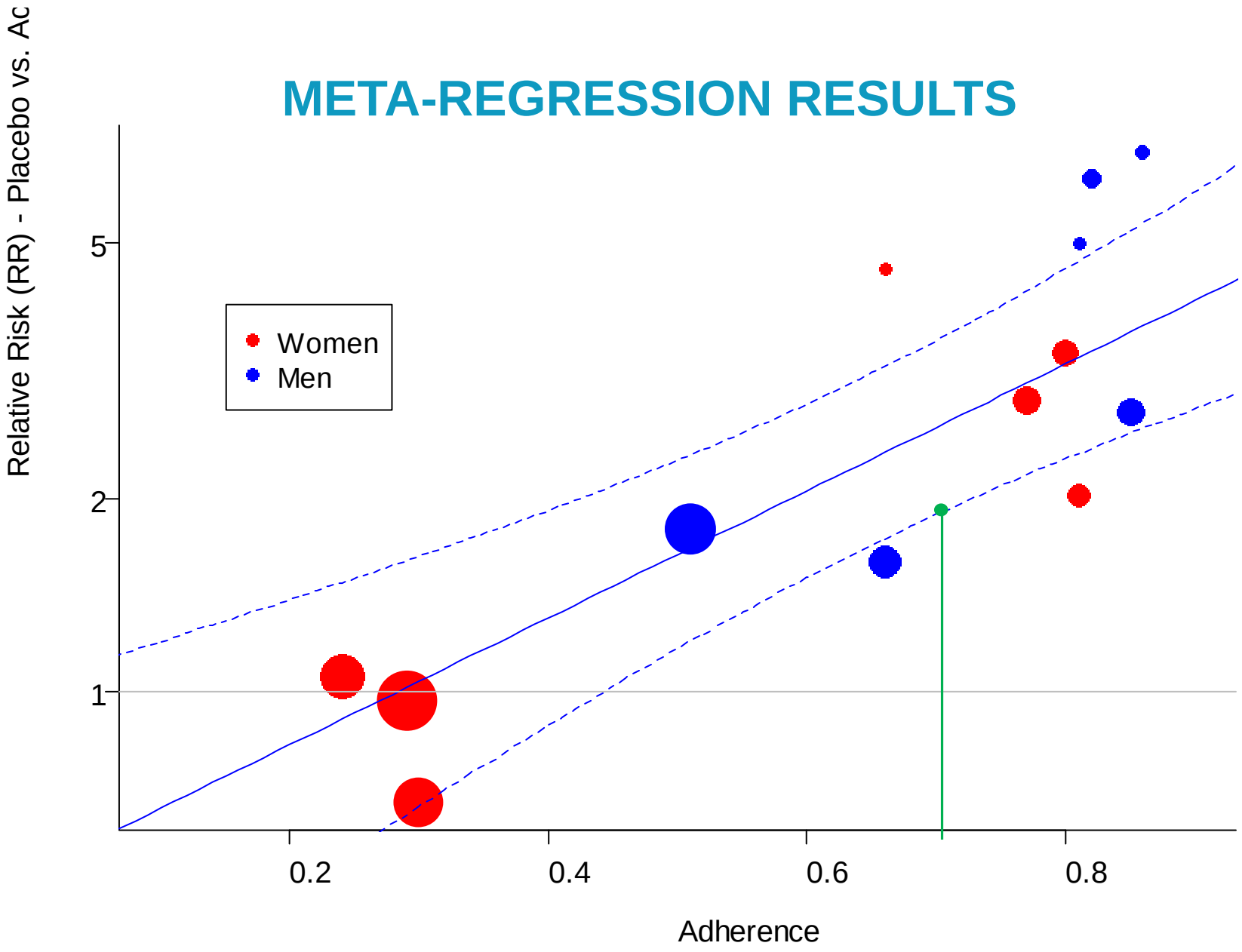



META-REGRESSION RESULTS
Relative Risk (RR) - Placebo vs. Ac
5
2
1
Women
Men
0.2
0.4
0.6
0.8
Adherence

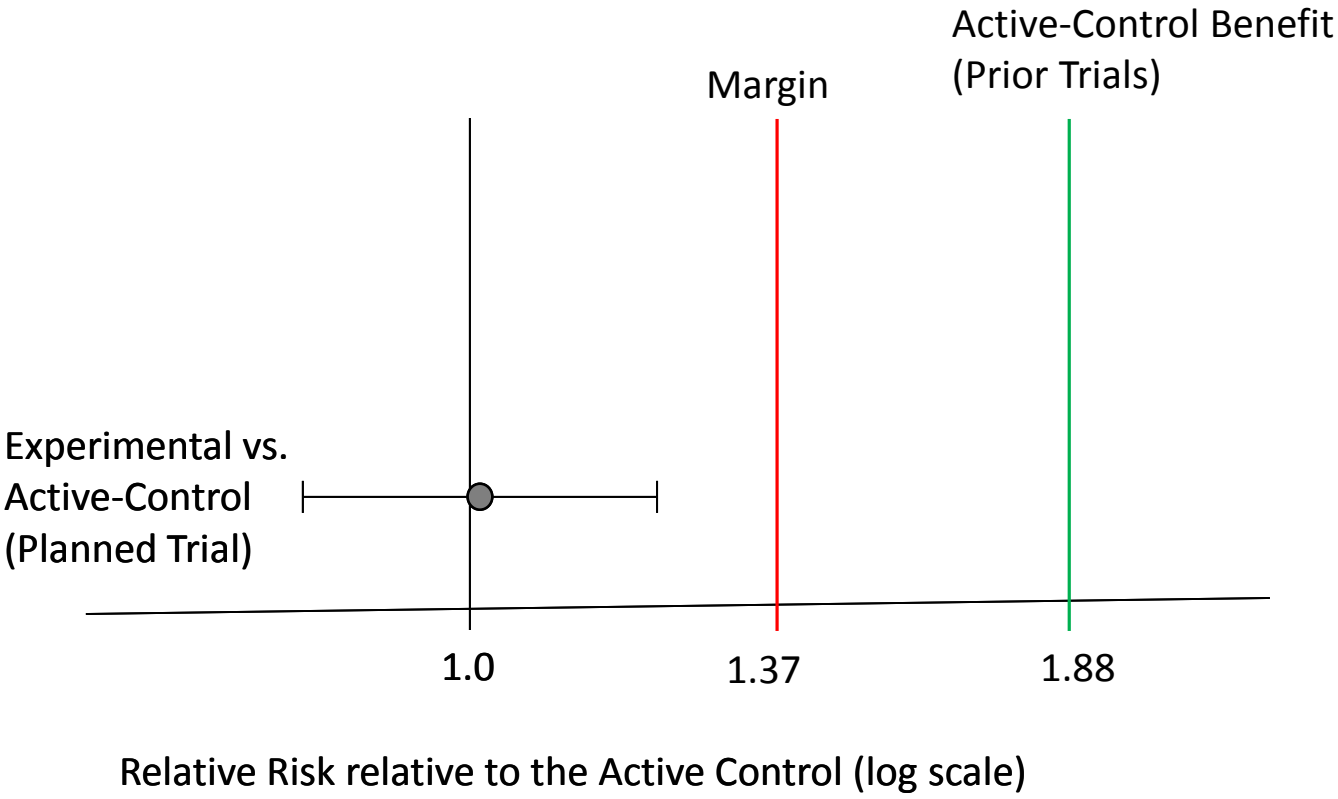

META-REGRESSION RESULTS
Relative Risk (RR) - Placebo vs. Ac
5
2
1
Women
Men
0.2
0.4
0.6
0.8
Adherence

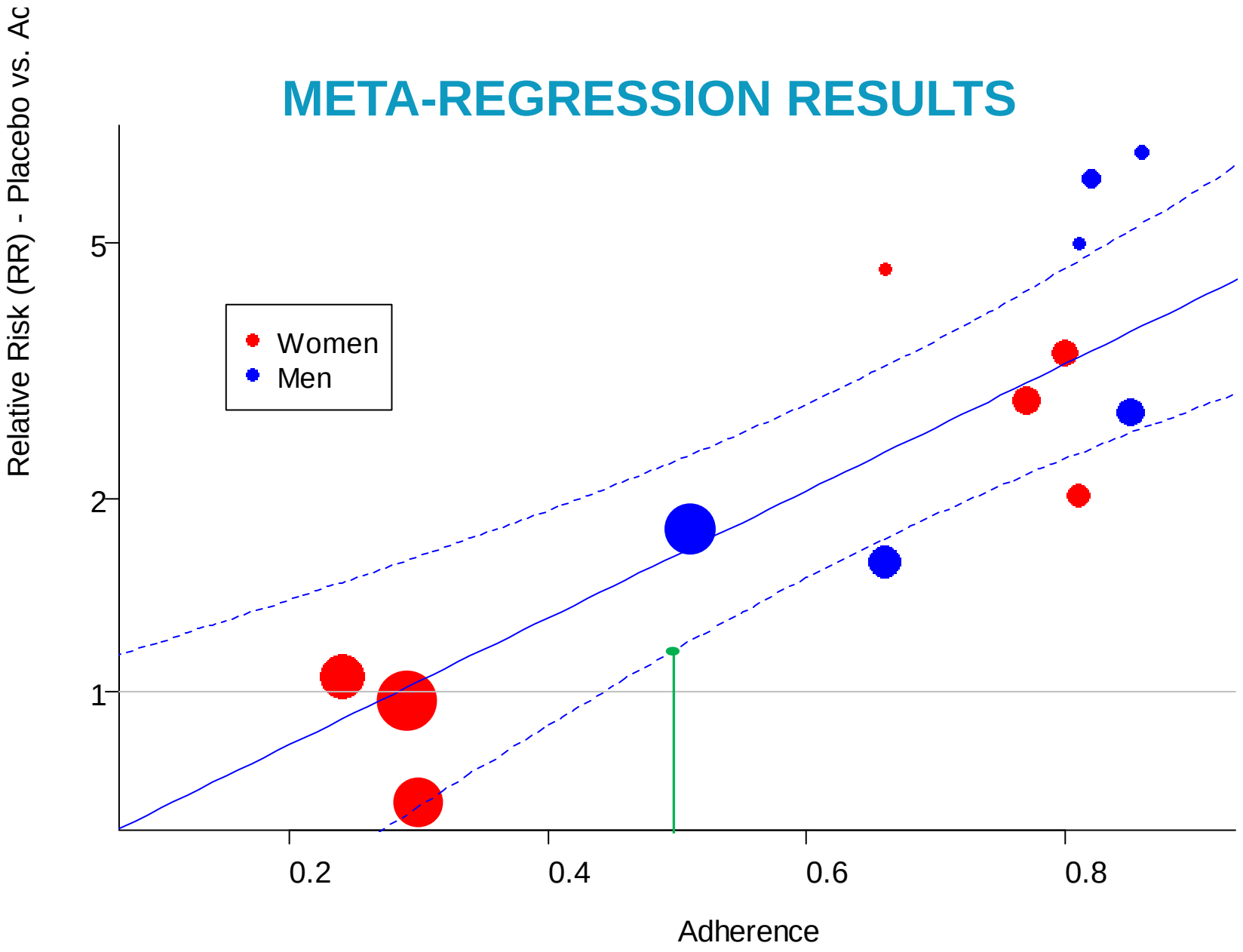
NON-INFERIORITY MARGIN – 60% ADHERENCE



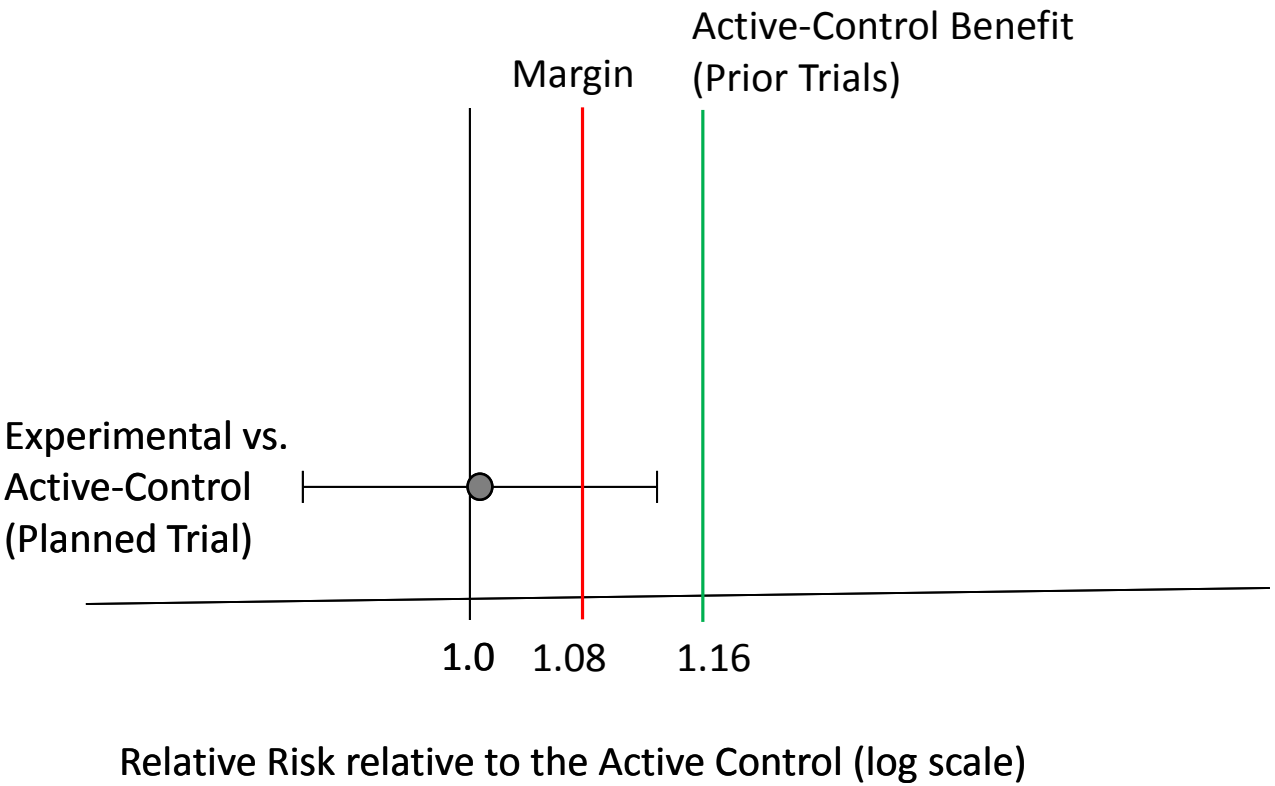

META-REGRESSION RESULTS
Relative Risk (RR) - Placebo vs. Ac
5
2
1
Women
Men
0.2
0.4
0.6
0.8
Adherence

NON-INFERIORITY MARGIN – 70% ADHERENCE




META-REGRESSION RESULTS
Relative Risk (RR) - Placebo vs. Ac
5
2
1
Women
Men
0.2
0.4
0.6
0.8
Adherence

NON-INFERIORITY MARGIN – 50% ADHERENCE



Potential NI Margins

	Men		Women	
Adherence	TDF/FTC Benefit	NI Margin	TDF/FTC Benefit	NI Margin
0.4	< 1.0	1.0*	< 1.0	1.0*
0.5	1.17	1.08	1.15	1.07
0.6	1.5	1.23	1.38	1.17
0.7	1.89	1.37	1.62	1.27
0.8	2.3	1.52	1.89	1.37

* Superiority required

Monitoring

- Interim adherence assessment
- Meta-regression model could be used to:
  - Determine whether planned margin is appropriate
  - Adjust early stopping rules to make trials more efficient
- Research underway to determine how best to do this

Summary

- It will be increasingly common to see non-inferiority trials for HIV prevention
- Essential to consider adherence levels in the target population when planning and monitoring these trials
- Meta-regression methods can provide NI-margins tailored to the target population

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