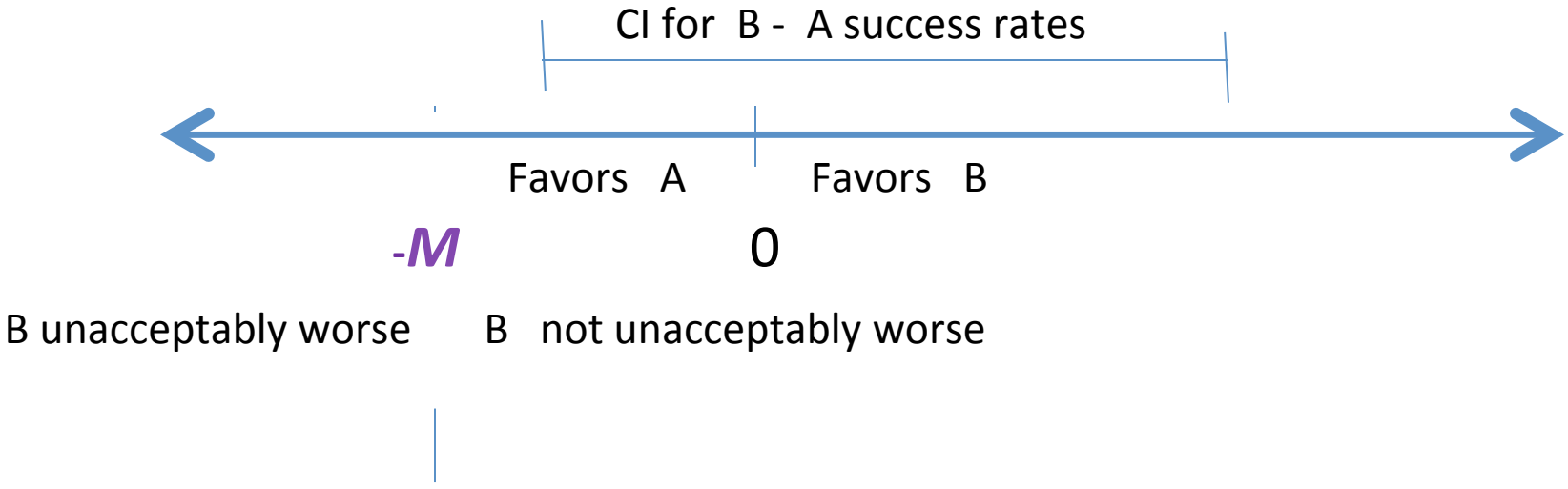
Discordant MIC Analysis: Testing for Superiority within a Non-inferiority Trial

Dean Follmann, Erica Brittain, and John Powers
National Institute of Allergy
and Infectious Diseases
November 19, 2014

Current Anti-infective Drug Landscape

- Efficacy typically demonstrated with non-inferiority trial: comparing new Drug B to control Drug A

- CI of difference in success rates needs to exceed some ***margin* M**



Dual Goal

- Goal 1: Demonstrate Drug B is active (better than placebo)
  - Established indirectly: must know magnitude of A's benefit over placebo, M_1. B must then be within M_1 of A

- Goal 2: Demonstrate that Drug B is similar to Drug A
  - By showing difference is less than M_2, which is *clinical-judgment* based acceptable loss in efficacy

- To satisfy both goals: $M=\min(M_1,M_2)$
- With current approach: if no historic data sufficient to set M_1, no way forward

A Pharmacometric-based Approach to Estimate M_1

- Ambrose et al (2012)

- Using a one arm sample of patients treated with Drug A: model and estimate success rates as function of AUC:MIC
  - Estimate success at very high AUC:MIC value
  - Estimate success at very low AUC:MIC (proxy placebo)
  - Difference is considered the treatment effect of A vs placebo

- Lower bound of a 95% CI of this synthetic treatment effect can serve as an estimate of M_1

More on One Sample Approach

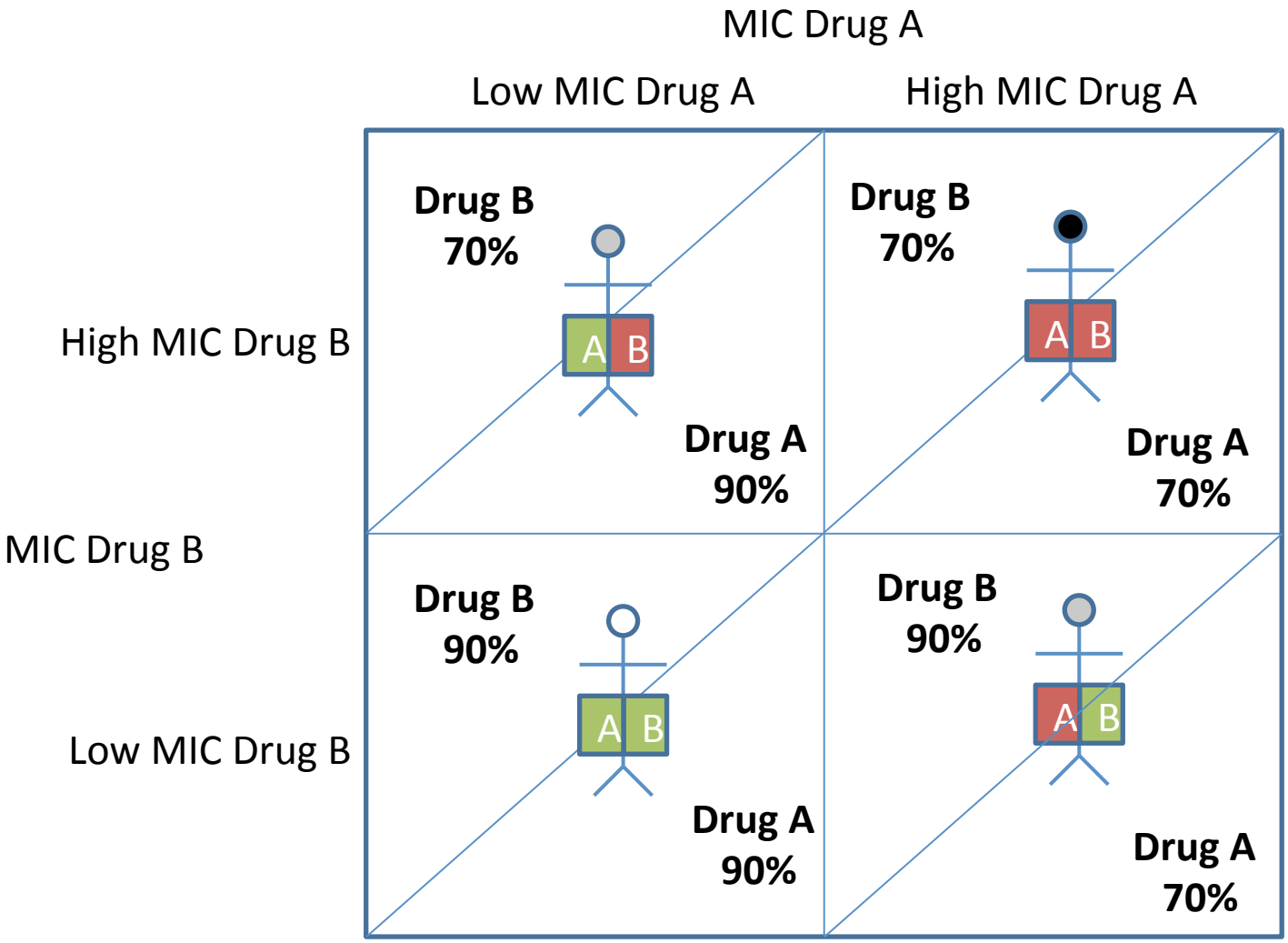
- But, not a randomized comparison
  - High AUC:MIC patients may be healthier.
  - Low AUC:MIC may identify pathogens that are harder for natural immunity to defeat
  - Crux: we do NOT know how these same patients would do with placebo

Drug	Success Rate with Very High AUC:MIC	Success Rate with Very Low AUC:MIC
A	**90%**	**60%**
Placebo	**?**	**?**

Can We Improve This Strategy with Randomization?

- Hidden within an ordinary non-inferiority anti-infective trial are precious sub-trials well placed to show superiority

Consider Four Interesting Subgroups: Where Overall Success Rates are 80% in Both Arms



Key Idea: Test for Superiority of B to A Where Most Likely to Find it

- Potentially get evidence of B's activity DIRECTLY within the trial!
  - Test superiority of Drug B to Drug A in the discordant MIC subgroup of patients – who are highly susceptible to B and not so susceptible to A
  - Then, conclude B is active – one of our dual goals
  - Don't need that hard-to-get historic evidence about the magnitude of A's benefit over placebo, M_1!
  - Required assumption: A is not worse than placebo in subgroup
    - remember A is approved
- (Focus now on MIC as our marker of success prediction
  - AUC:MIC is trickier – more on this later)

Proposed Demonstration of Efficacy when M_1 Unknown

- Recall dual goal:
  - B has activity and B is similar in overall efficacy to A
- Decide on a clinically acceptable **margin M_2** e.g. **10%.**
- Efficacy supported if
  - Overall NI margin of **10% (M_2)** is met AND
  - Good outcome on pre-specified test of superiority of B over A shown in patients for whom it is *a priori* most likely
    - High MIC-A/low MIC-B subgroup
    - The patient in the ``sweet spot" (using Discordant MIC model)
    - Patients with high MIC-A (e.g., Advisory Committee 2012: Televancin vs Vancomycin results in s. aureus and MIC-V>1; p<.05)

Discordant Regression Method

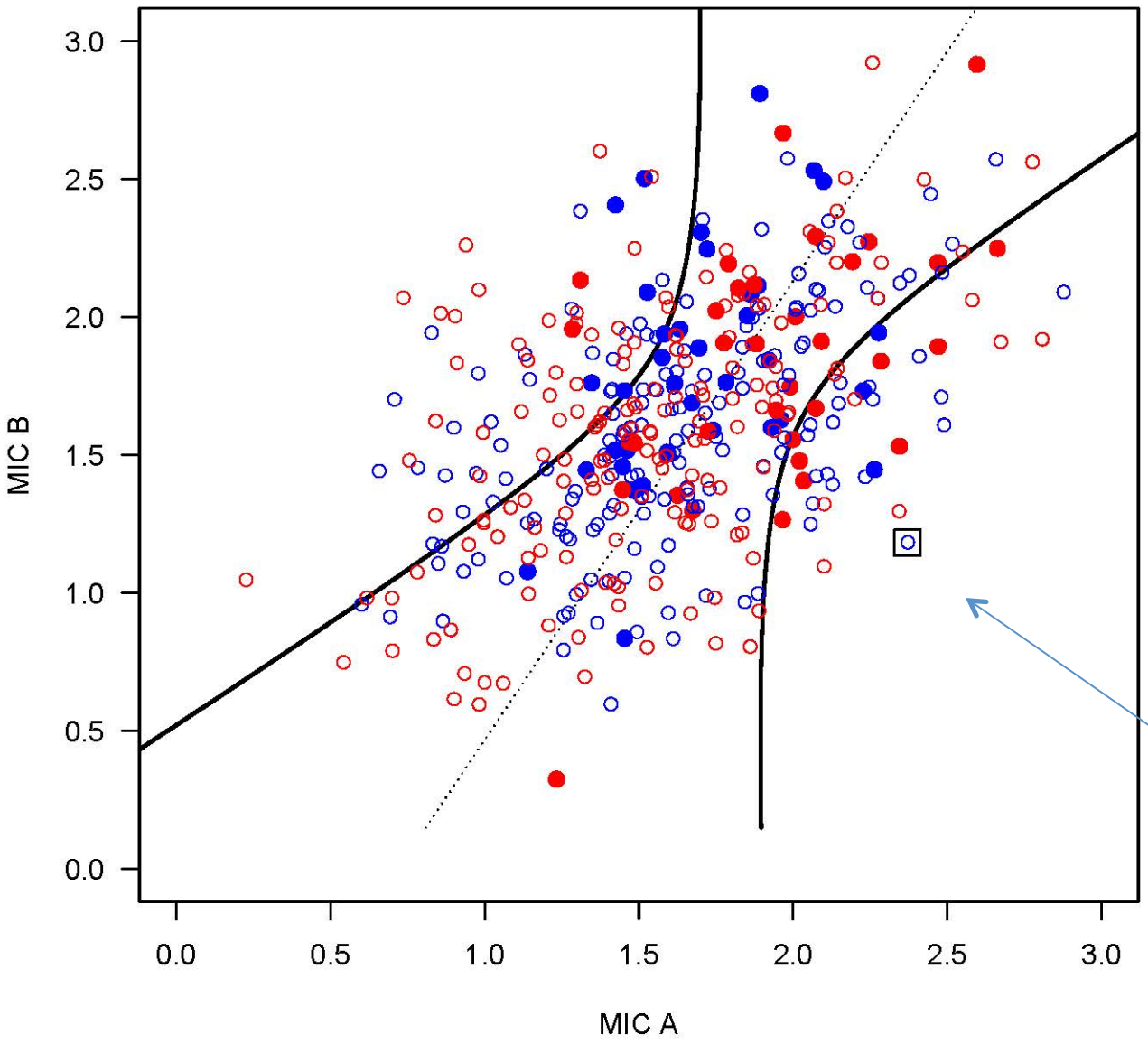
- Only analyzing patients in the Low MIC-B/High MIC-A subgroup is likely to be statistically inefficient
- So, use all data with logistic regression to estimate response surface
- Log odds of success on B to success on A:

$$\beta_0 + \beta_1 Z + \beta_2 \text{MIC-A} + \beta_3 \text{MIC-B} + \beta_4 Z\ \text{MIC-A} + \beta_5\ Z\ \text{MIC-B}$$

  - Z= 1 drug B (0 Drug A)

- Test H_0: $\beta_1 + \beta_4 a_0 + \beta_5 b_0 = 0$
  - Procedure is point-wise, so need to pre-specify a single "sweet spot" (MIC-A=a_0, MIC-B=b_0) to have correct Type I error rate

- Simulations done with 200/arm, range of correlations between MIC-A and MIC-B, range of relationships between MIC & outcome



Sweet Spot
B beats A
p = .01

Patient Got Drug B and had Success

Patient got Drug A and Failed

Simulation Study Results Suggest Method Will Have Reasonable Power When:

- Clear relationship *in the trial*:
  - Between MIC-A and success on Drug A, and
  - Between MIC-B and success on Drug B
- Little relationship between response and MIC to *other* drug
- MIC-A and MIC-B are not highly correlated
- Selected sweet spot is a powerful spot to test

Advantages

- Encourages sponsors to design for superiority
  - So that rigor is rewarded instead of punished
  - Try to avoid patients who cure spontaneously or who do not have bacterial disease
- Get *direct* evidence that B has activity, instead of relying on external data
  - External data might not be relevant

- But, challenges remain…

Challenge 1: How to use AUC:MIC ratio?

- AUC: MIC has (much?) stronger relationship to success than MIC
  - Much greater variability within a trial
    - (Side Question: are patients with high MIC to his/her randomized drug tossed out? If yes, is it compatible with ITT?)

- Problems with using AUC:MIC
  - AUC is a post-baseline covariate
  - AUC to A inherently missing in those randomized to Drug B, and vice versa
  - Currently only measured in subset of B – and none in A

Challenge 1: Using AUC:MIC

- Solutions?

- Augmentation:
  - Crossover patients twice to get their AUC to each drug at end of regular follow-up
    - but this requires (strong & untestable) assumptions

- Baseline models (More promising?):
  - Could use baseline characteristics to predict AUC
    - Prediction models exist, but how relevant?
    - If AUC were measured in both arms, could develop within-trial predictions of AUC using baseline data (age, gender, weight,…)

Challenge 2: Selection of Sweet Spot

- The discordant MIC regression analysis is point-wise, and thus to protect Type I error rate, we need to pick a single point *a priori*
- Could use a simultaneous approach to testing, but this is non-targeted and thus much more conservative
- Simple approach: pick observed value that is closest in Euclidean distance to (Max observed MIC-A, 0) point
  - But depending on the true model, this may not be optimal point
- Alternative: adaptive selection of sweet spot, using (half) blinded mixture models looks very promising

Challenge 3: Feasibility

- Enhance power by pooling multiple studies
  - Should not increase usual sample size requirement
- Feasibility probably highly dependent on the context of each given study setting. Evaluate power in Phase 2:
  - Relationship between MIC and outcome within arm
  - Also explore viability of using AUC:MIC

Summary

- New paradigm for demonstrating efficacy if inadequate historic data to know treatment effect of control drug A
  - Pick a clinically acceptable margin for total sample PLUS
  - Test for superiority where it's most likely to be present

- Encourages a careful design/conduct to show superiority

- Current work:
  - Extension to AUC:MIC
  - Better procedures / sweet spot
  - Consideration of real world feasibility

- Follmann D, Brittain E, Powers JH: Discordant minimum inhibitory concentration analysis: a new path of licensure for anti-infective drugs. *Clinical Trials* 2013; 10: 876-885