Some Thoughts on Implementation of E9(R1)

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Regulatory Context

- E9(R1) is authoritative (means what it says)
  - But not yet definitive (will be revised)
- FDA policy will conform to E9(R1) as revised
  - Possible regional guidance
  - Not yet under way
  - Formal process for dissemination
- No new research to be presented
- So what is the purpose of this talk?
  - Points to consider

Comparisons

- Causal estimand means treatment effect
- Treatment effect means comparison of outcomes under different treatments
  - In the same subjects (Rubin causal model) or …
  - In comparable subjects
- Kinds of comparison
  - External comparisons
  - Nonrandomized comparisons
  - Randomized comparisons

Kinds of Comparison

- External comparisons
  - To something not in study
  - Very, very hard
- Nonrandomized comparisons
  - Between not necessarily comparable groups
  - Very hard
- Randomized comparisons
  - Between necessarily (on average) comparable groups
  - Easy, but not always exactly what is wanted

Kinds of Comparison

- External comparisons
  - Very, very hard, but sometimes needed
- Nonrandomized comparisons
  - Very hard
- Randomized comparisons
  - Easy, but not always exactly what is wanted
  - But there may be more choices than are apparent
- Nonrandomized comparisons
  - An easy one!

External Comparisons

- Historical controls
  - Because the randomized study is impractical or unethical
  - Rely on constancy of outcome
- Noninferiority—Putative placebo
  - Because the randomized study is impractical or unethical
  - Rely on constancy of effect (of comparator vs. placebo)
- If no rescue (“hypothetical”)

If No Rescue

- Not in patients not needing rescue
- Rather, in a study (world?) without rescue
  - Is this relevant?
    - Sometimes
    - Compare to noninferiority
- What constancy assumption is needed?
  - Quasi-internal comparison (before rescue)
  - What sensitivity analysis is needed?
- Widely known methods may not be enough

Nonrandomized Comparisons

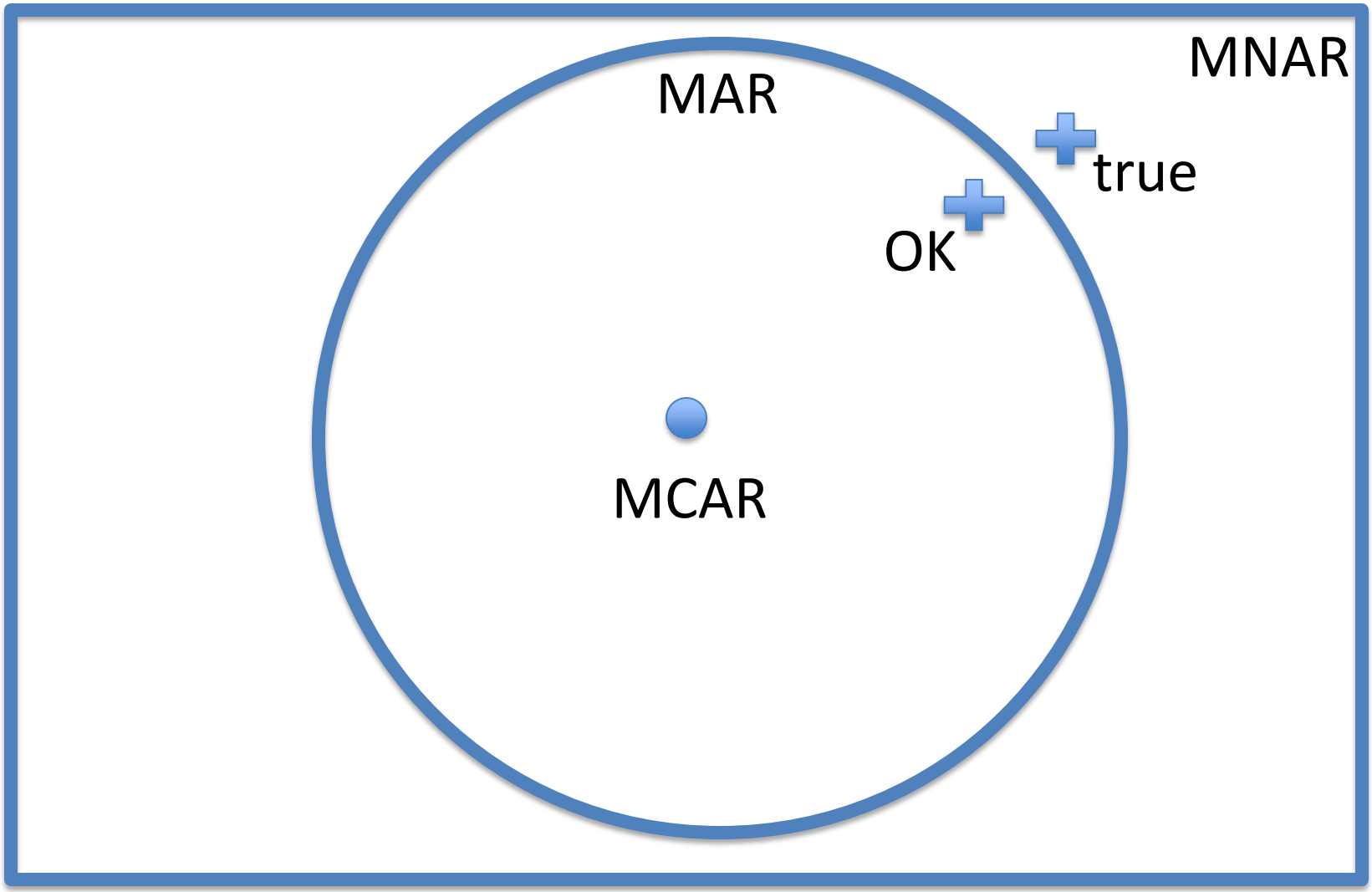
- Goldilocks epidemiology
- Adjusting for confounders
- What to adjust to

Goldilocks Epidemiology

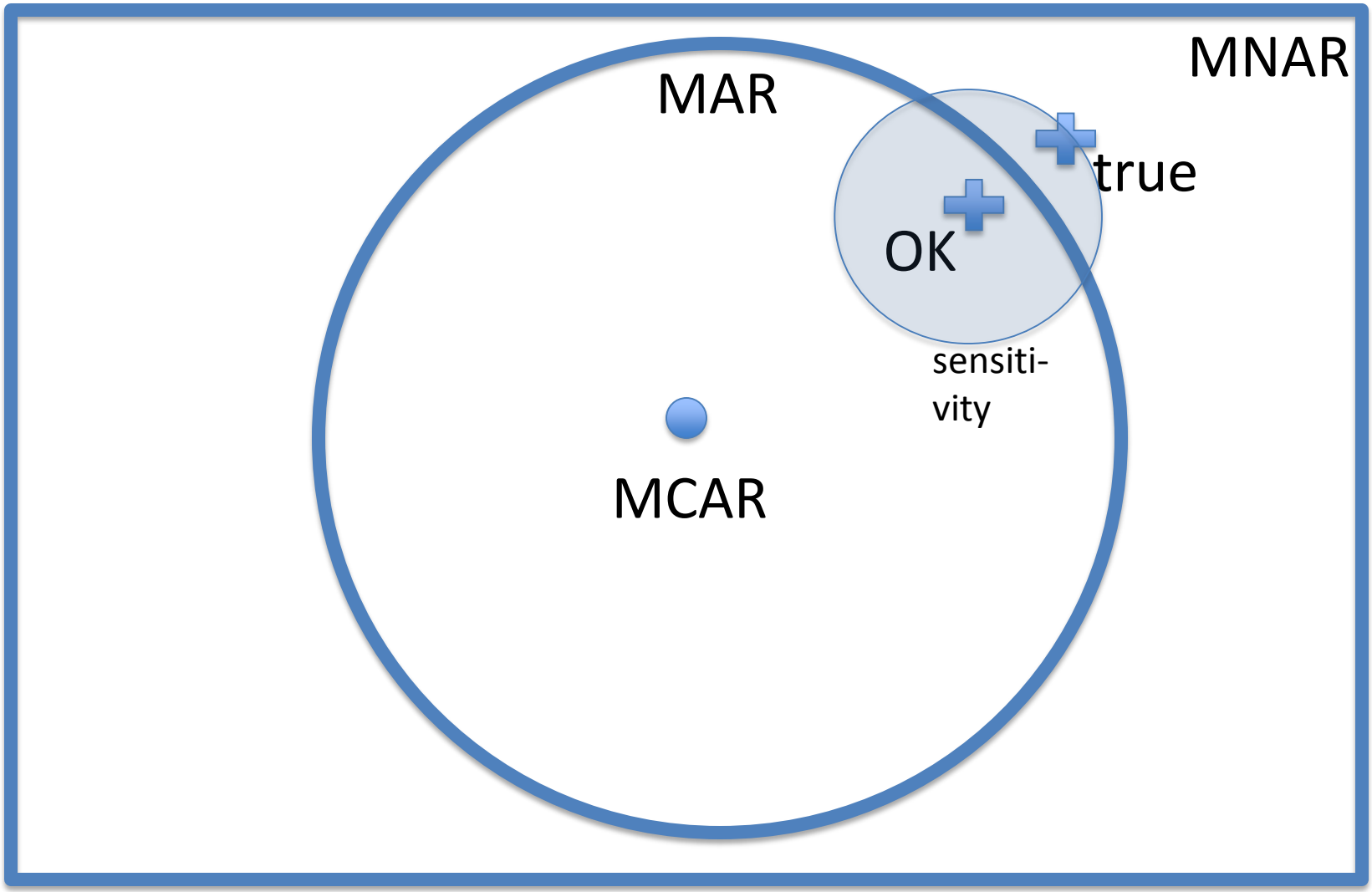
MCAR

Goldilocks Epidemiology

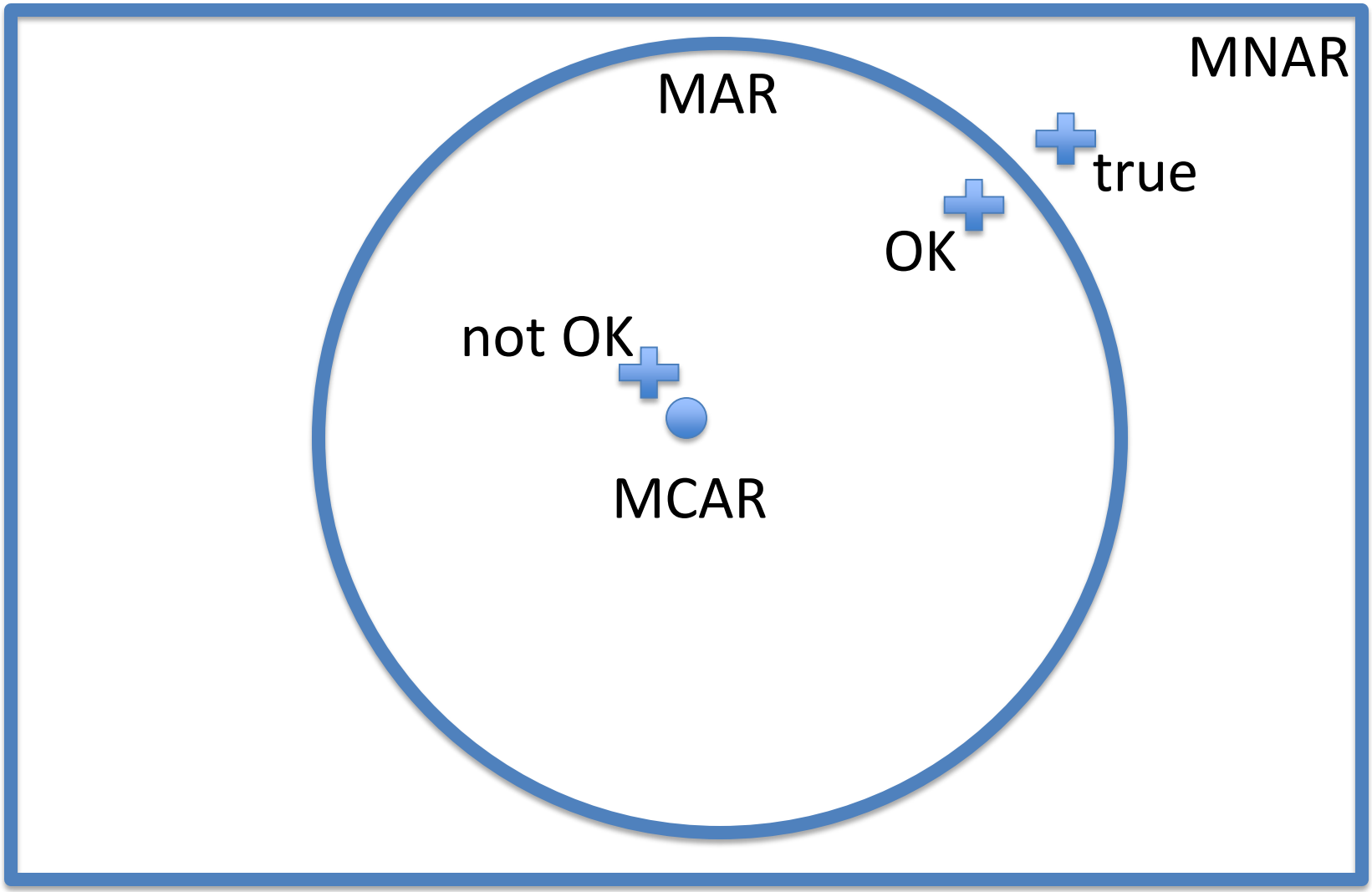
Goldilocks Epidemiology



Goldilocks Epidemiology



Goldilocks Epidemiology



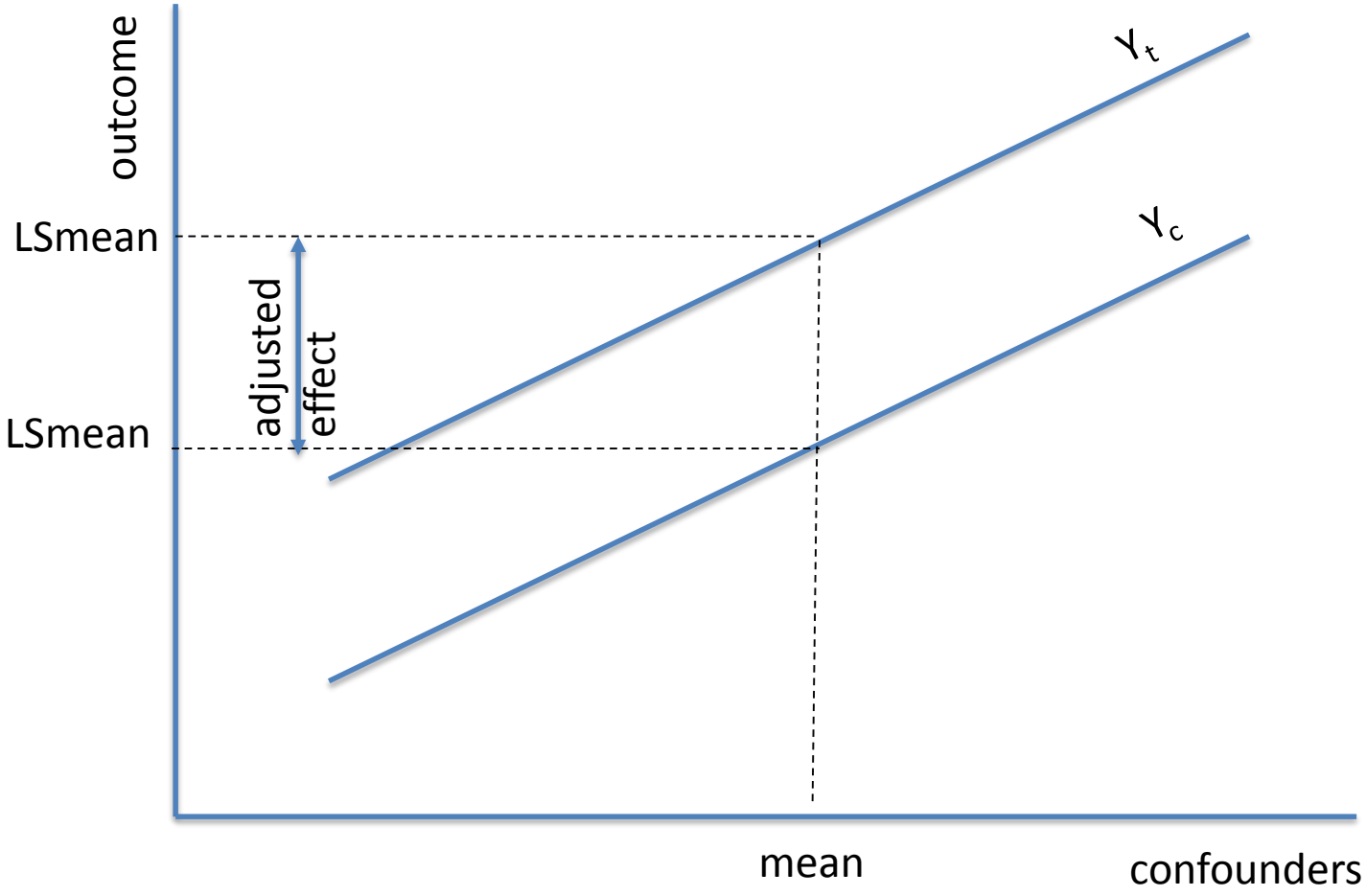
Nonrandomized Comparisons

- Are hard
- Are necessary in epidemiology
  - May not be necessary in randomized trials even with dropouts
  - Because this is not missing data
- Adjust for everything in sight
- Then worry about what's not in sight
- No unmeasured confounders means
  - Measured, and
  - Correctly modeled

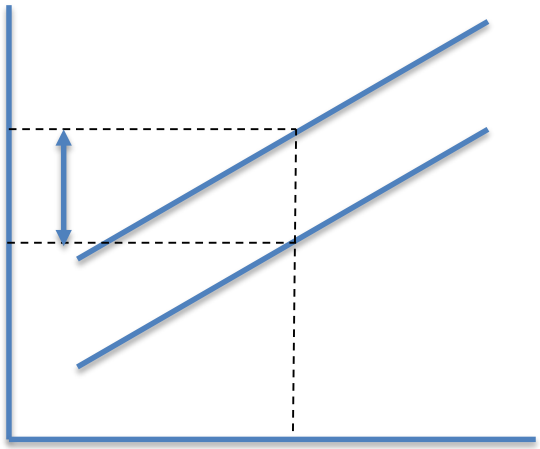
Nonrandomized Comparisons

- Can use MAR techniques
- Can't just hypothesize MAR

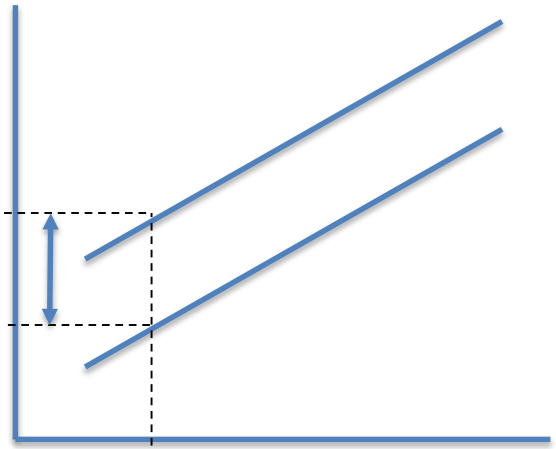
What to Adjust to



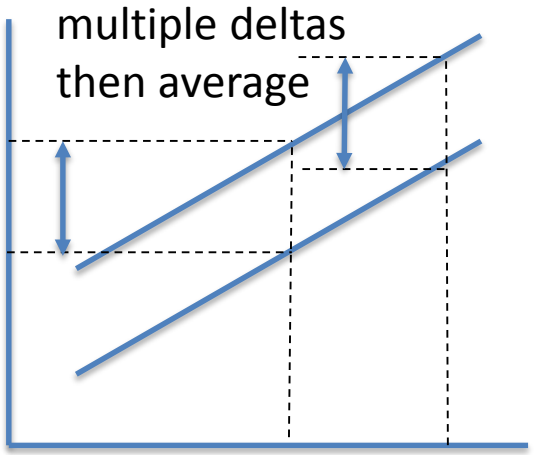
What to Adjust to



mean



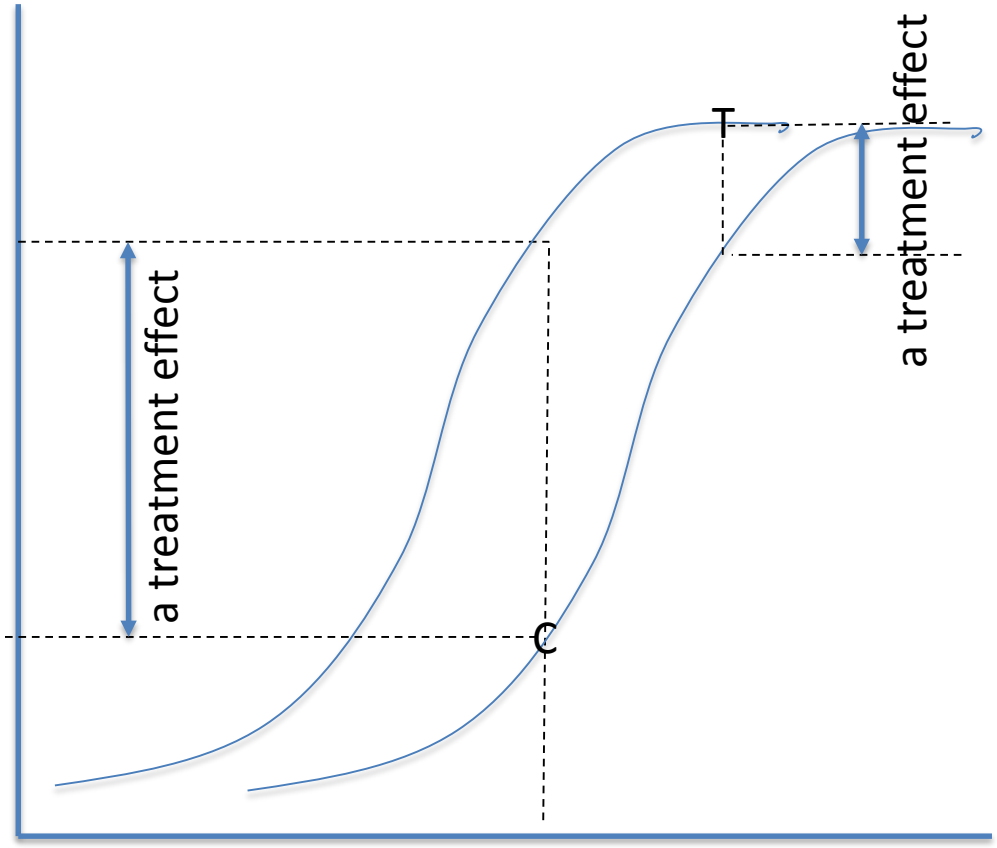
not mean



It doesn't matter!

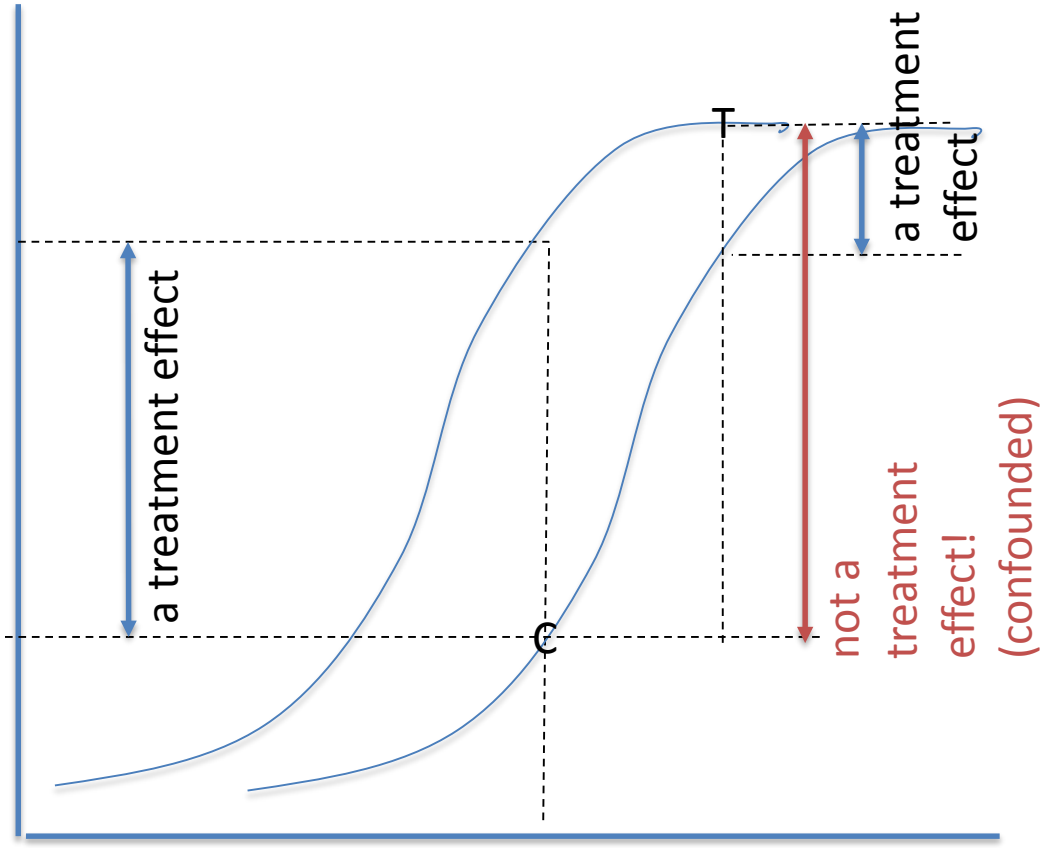
Average Treatment Effect, Plug-In Estimator

- Fit curves for treatment groups
- Plug in some observed values of confounders
- Calculate deltas
- Average deltas



Which Observed Values of Confounders to Adjust to?

- Matters some when treatment effects vary with confounders
- Differently weighted averages of valid treatment effects
- But not adjusting gives confounded effect



What to Adjust to?

- Effect among the treated
  - Population that would adhere to test drug, whether or not they would adhere to control
  - Other populations possible
    - If all patients adhered
  - See SBR paper
- Important thing is to adjust
  - Because it's nonrandomized comparison
  - Doesn't matter very much to what
  - Do not accept an informal interpretation of "if all patients adhered"
    - Sounds more like intent-to-treat, but it isn't (nonrandomized)
    - Different kind of hypothetical

Randomized Comparisons

- Classic—ITT
- Modified

Intent to Treat

- Don’t redefine it
  - Get all primary outcome data
  - But missingness is inevitable, so …
  - ~~Just use what you have without exclusions~~
  - Serious follow-up and adjustment
- Minimize missing data
  - Minimize loss to follow-up
  - Do not minimize nonadherence

Modified Randomized Comparisons

- While on treatment
- Dropout as failure

While on Treatment

- Last observation
  - Not carried forward
- Average observation
  - ≈ MMRM main effect
  - Not MAR (wrt simple model)
  - Not de jure
    - if that exists, …
    - MMRM still doesn't estimate it …
      - Except under MAR
      - Maybe even under MAR (see SBR paper)

While on Treatment

- Fine statistically
  - Unbiased (but …)
  - Preserves Type I error (but …)
- Meaningful estimand/hypothesis?
  - Yes—Discontinuation due to cure
  - No—Discontinuation due to failure (toxicity/lack of efficacy)
    - Especially when some failures are given good scores and others bad scores
  - Measure benefit!

Dropout as Failure

- Need not dilute treatment effect
- Need not lose much information
  - Possible gain in information compared to handling as “missing” (but see Cro et al.)
- Trimmed mean, rank methods
- Compare to survival
  - Don’t treat survival as “missing” time to event
  - Don’t impute time of death for surviving patients!
  - Dropout considered as failure is censoring/competing risk, not missingness

Easy Nonrandomized Comparison

- Nonrandomized comparisons are hard
  - Because “no measured confounders” is a very strong assumption
- But there might be an easy one
  - Be suspicious!

Easy Nonrandomized Comparison

- Suppose:
  - ITT effect (all patients followed and counted) is 5
  - Half the patients on active drug adhere
  - It doesn't matter whether you adhere to placebo
    - Not: placebo nonadherents are like placebo adherents
  - You have to adhere to active drug for it to work
- Then the effect in adherents is diluted by the non-effect in nonadherents
- How much is it diluted?

How Much Dilution?

- ITT effect =
  (proportion of adherents)(effect in adherents) +
  (proportion of nonadherents)(effect in nonadherents)
  = (0.5)(y) + (0.5)0 = 5
- y = 10

Two Questions

- Why follow after discontinuation if interest is in adherent subjects?
- How can nonrandomized comparisons ever be easy?

Nonrandomized Comparison Hard Because …

- Need to adjust for confounders
- What is the best confounder to adjust for?

Nonrandomized Comparison Hard Because …

- Need to adjust for confounders
- What is the best confounder to adjust for?
  - Good predictor of (placebo) outcome
- But there is perfect predictor of placebo outcome in dropouts!
  - If they are followed

Estimands/Effects/Comparisons

- External comparisons
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References

- Cro S, Carpenter JR, Kenward MG. Information-Anchored Sensitivity Analysis: Theory and Application. arXiv preprint arXiv:1805.05795
- Permutt T. Effects in Adherent Subjects. Statistics in Biopharmaceutical Research. 2018 (what to adjust to, what MMRM estimates)
- Permutt T, Hebel JR. Simultaneous-equation estimation in a clinical trial of the effect of smoking on birth weight. Biometrics. 1989:619-22 (easy nonrandomized comparison)