Defining Treatment Effects: A Regulatory Perspective

Some Thoughts on Implementation of E9(R1)

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Three Questions and an Answer

- Words or numbers?
- Treatment policy
  - Are you going to let them stop doing it?
  - Are you going to make us do it?
- Principal stratification—Seriously?
- Robust and easy per-protocol analyses

Words or Numbers?

- Framework—Words
- No new methods—No numbers
- Can we agree on statistical methods first, and write about estimands later?

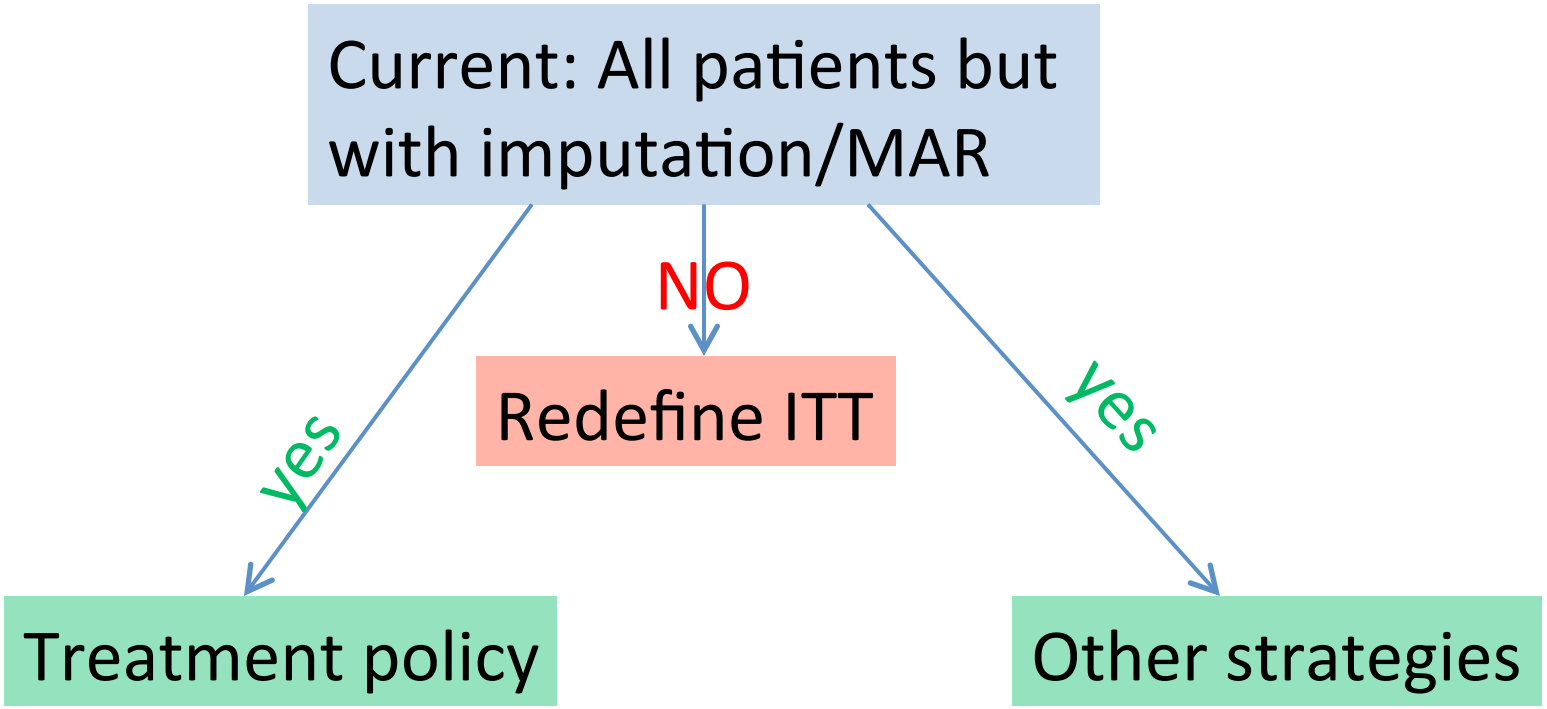
Words or Numbers?

- Can we agree on statistical methods first, and write about estimands later?
- No.
- The framework is important, but …
- We also want different methods
- Words *and* numbers
  - Hypothetical ≠ MAR

Treatment Policy

- Are you going to let them stop doing it?
- Are you going to make us do it?
- "Outcome" studies—Keep doing it
- "Symptom" studies
  - "In symptomatic settings, it is not the usual practice to continue to assess effectiveness in patients after they have stopped taking the assigned treatment (ITT approach)" (Temple & O'Neill 2012)

Which Way?


Current: All patients but with imputation/MAR
NO
Redefine ITT
yes
yes
Treatment policy
Other strategies

Treatment Policy ("Symptom")

- Are you going to let them stop doing it?
  - They never started
- Are you going to make us do it?
  - You have to stop pretending to do it
  - Do it or …
  - Do something else and say what

Principal Stratification

- Impractical?
- Irrelevant?

Impractical?

- Hard to understand
- Hard to satisfy assumptions
- Hard to prespecify

Hard to Understand?

- Not really
- Part of *treatment effect* is to make subjects continue or discontinue
  - {continue, discontinue} X treatment → principal strata
- If you can't tell me what you did with subjects who would discontinue only on test drug, *I* won't understand
  - I.e., principal stratification is an essential part of the *discussion,* even when not of the solution

Hard to satisfy assumptions

- Yes, really
- Sometimes easier than MAR

Antarctica

- Some subjects move for reasons completely unrelated to treatment
- MCAR, so …
- Can use completers

Antarctica

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- Right?

Antarctica

- Some subjects move for reasons completely unrelated to treatment
- MCAR, so …
- Can use completers
- Right?
  - No, not necessarily MCAR
  - Yes, can use completers …
  - To estimate effect in principal stratum

Hard to prespecify

- Yes
- Consider prespecifying modeling algorithm rather than model?
- With cross-validation
- But maybe it is impractical
  - Maybe selection modeling is not better than outcome modeling
    - Or maybe it is
    - Or maybe do both (double robust)
  - But modeling is modeling
    - Looking hard is a feature, because it is hard
    - Don't redefine ITT

Irrelevant?

- Want
  - Pharmacologic effect or …
  - Per-protocol effect or …
  - "Efficacy" (vs. "effectiveness")
- This is difficult to define
  - Part of *treatment effect* is to make subjects continue or discontinue
- Principal stratification (uniquely?) can yield precise definitions
- It is hard, maybe impractical
  - Can see it's hard (good!)
  - Easy ways are not easy

Robust Per-Protocol Analyses

- Not analyses of per-protocol set
- Crosscountry method (Permutt and Li 2017)
- Undilution method (Permutt and Hebel 1989)

Not Per-Protocol Set

- Don't estimate population variance by sample variance
  - Because it's *biased*
- Don't estimate treatment effect by difference in means
  - Use ANCOVA
  - Because it's less *variable*
  - But estimates same estimand
- So don't estimate per-protocol effect by per-protocol dataset!

Crosscountry Scoring

- Start 7, count best 5
- If your (test) 5 beat my (placebo) 5, your team is faster
- Nothing *assumed* about other 2, they just don't count

But …

- Inefficient
  - Not very, even compared to no dropouts
    - Think about median
  - Not comparable to imputation
- Unfair
  - Not.
- Not clinically meaningful
  - Sometimes, but …
  - Are you sure the raw mean is more meaningful?
  - If the worst scores are important, you'd better get them

Undilution

- Assume …
  - All treatment effect due to taking active drug
    - No compliance effect in controls
    - No persistent effect in noncompliers
  - No one in control group takes active drug
  - (Sensitivity analysis needed)
- Results
  - Half of active group comply
  - Treatment policy effect is 5
- What is effect in compliers?

Treatment Policy Dilutes

- TP = P{comply} * {complier effect} +
  P{not comply} * {noncomplier effect}
- 5 = (0.5) * X + (0.5) * 0
- X = 10
- Undilute!

Robust Per-Protocol Analyses

- Exist
- Do not need to solve hard problem
- But don't use a bad solution to the hard problem instead of a robust solution to an easy problem

Summary

- Treatment policy
  - Yes or no
  - Not redefined
- Principal stratification
  - Maybe too hard
  - But you can see how hard it is
  - Therefore better than hard methods that look easy
- Robust per-protocol analyses are possible
  - If you don't try to do the hard problem