Development of Estimands for Acute Treatment of Major Depressive Disorder: *Keeping the New Mindset in Mind*

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--no conflicts of interest to disclose—
20min

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Introduction

- Framing the “Estimand Mindset”
- Overview estimand development
- Considerations in the MDD context
  - Case examples

The Estimand Mindset

- *Estimand* is clinical construct:

The "clinical thing" to be quantified

"A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared."

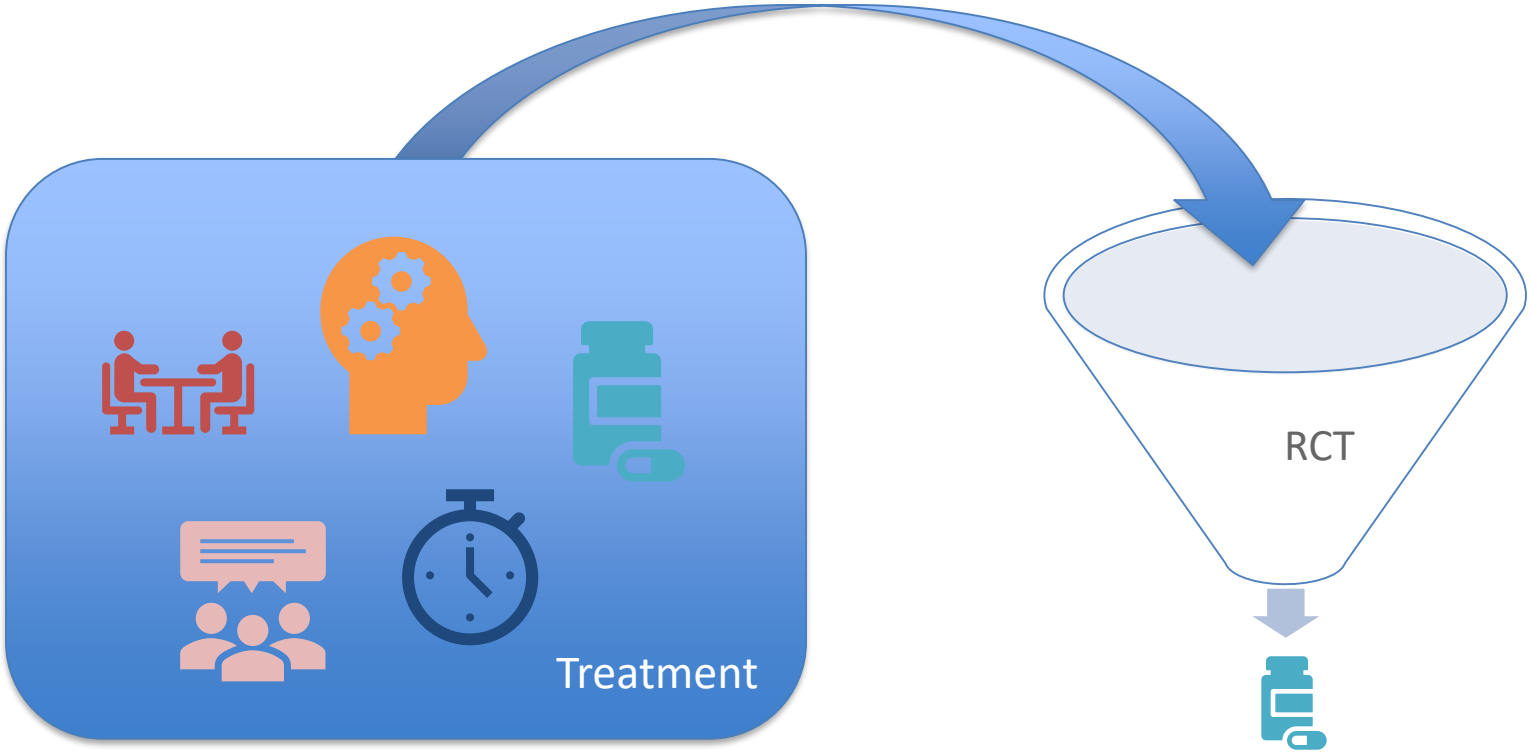
–ICH E9R1

What is a clinical thing?

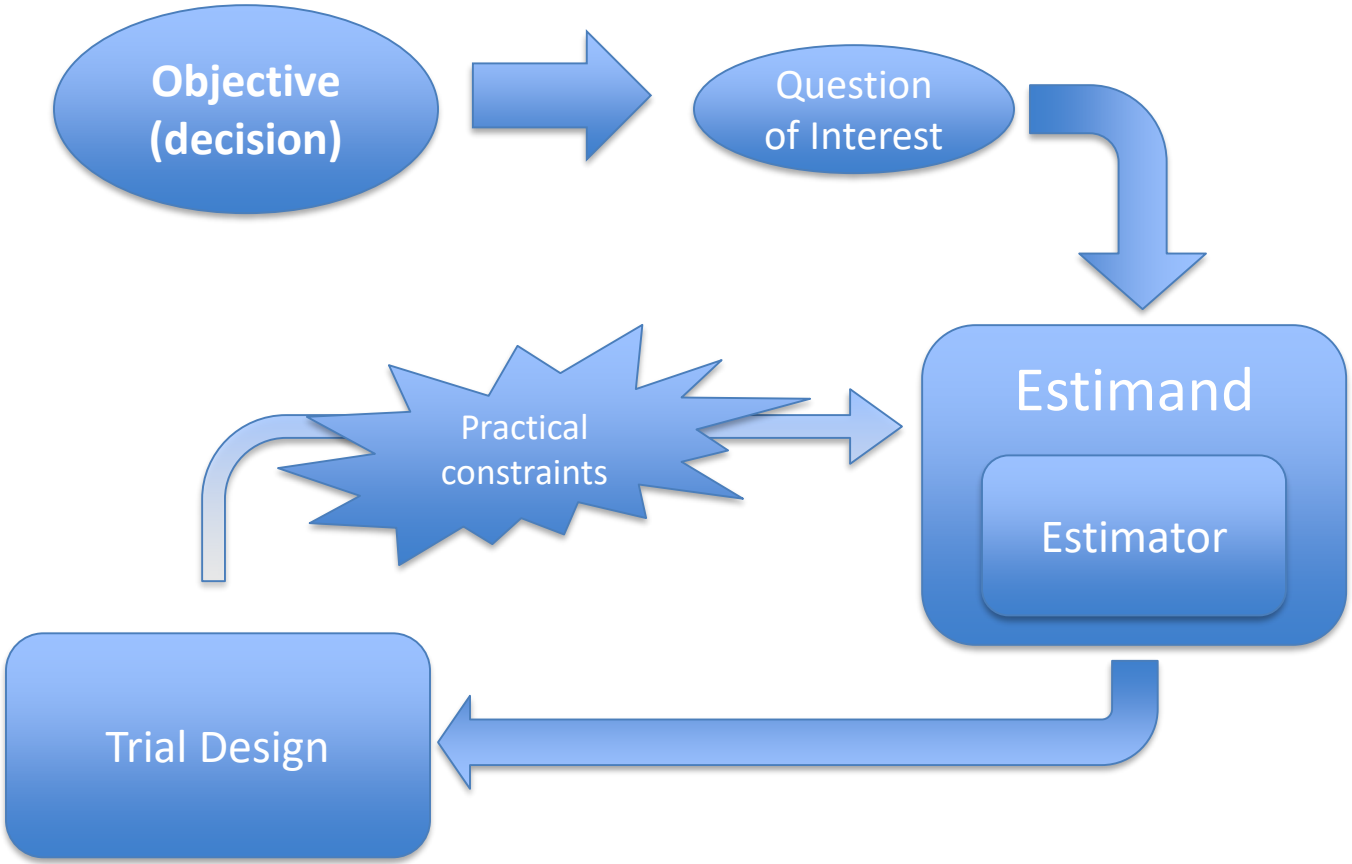
- Treatment effect
  - But…*"A pill won't do anything if you don't take it"*
- Treatment effect requires *a treatment*
- *So what is the treatment?*
  - *Depends what we want to know → estimand development (in a few easy steps)*

A treatment has lots of parts

an RCT is a filter to isolate the effect of one part



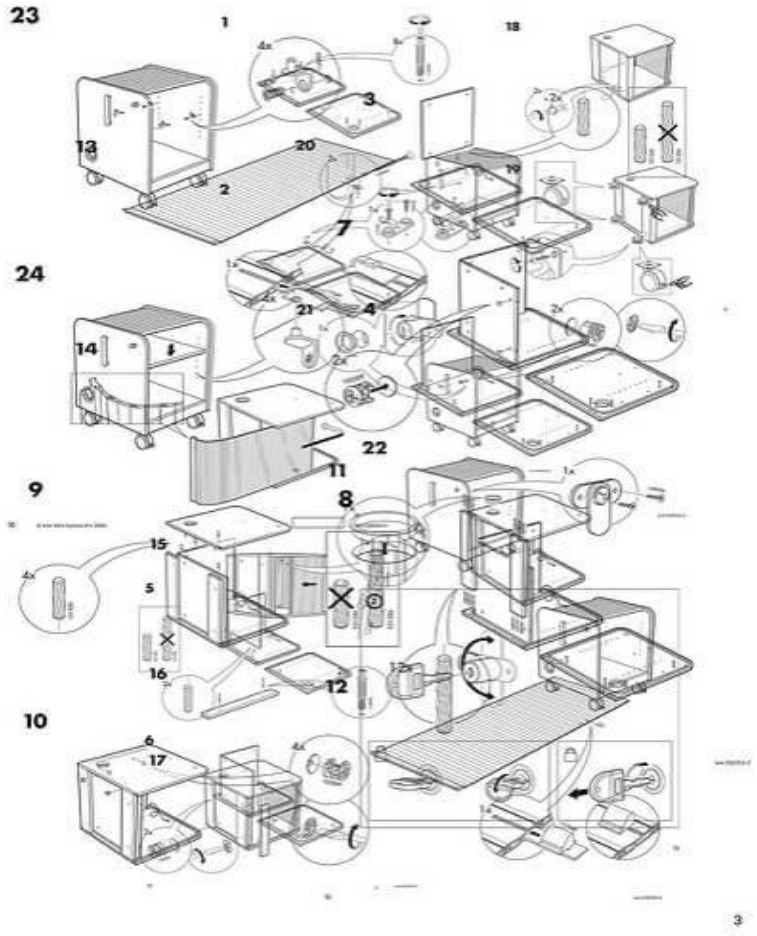
Primary Estimand Development:



5 Estimand Components:

- Define the targeted population of interest
- Select treatments (study interventions & comparators)
- Specify the measured variable (units of measurement of the estimate, e.g., MADRS points and timing – Change from baseline to Week 6)
- Identify intercurrent events (sources of interference with tool operation) relevant to estimand & select strategies for intercurrent events consistent with estimand objective
- Specify summary measure (population-level summary for the variable: e.g., difference in means between active and control groups)

Simple!



…just need to work out a few details

ISCTM Working Group Model Disorder: MDD

- Well studied
- Fairly understood background and endpoints
- But also many challenges:
  - high treatment dropout rates
  - high response in placebo arms

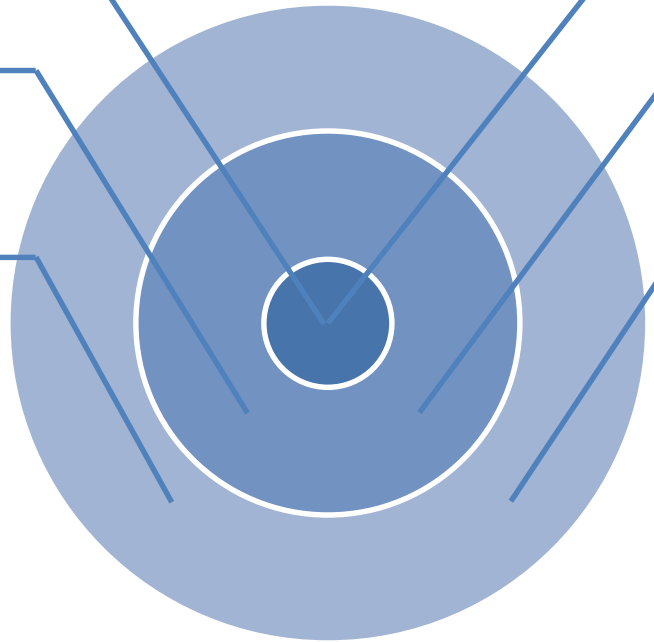
→ Many issues encountered in defining estimands in clinical trials of treatment for MDD can be generalized and applied to other clinical trials.

Developing an estimand to be quantified in a placebo-controlled acute MDD monotherapy trial

1. Identify primary decision

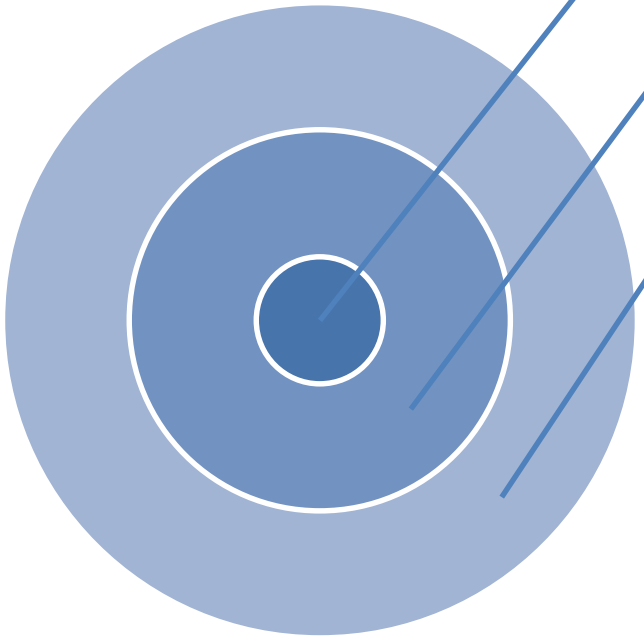
Primary Decision -- Nested Spectrum of Questions

Level of analysis	Decision to make
Biology: Effect of drug on 'disease'	Advance to P2/3? Dose selection
Medicine: Effect of drug on syndrome/disorder	Advance to P3? Dose selection Regulatory approval
Public Health: Effect of drug on patients/public	Regulatory approval Formulary inclusion



2. Define research question

Nested Spectrum of Questions – Relation to Regulation



Biology: Effect of drug on 'disease'

Medicine: Effect of drug on syndrome or disorder

Public Health: Effect of drug on patient/public

CFR §314.126 AWC studies

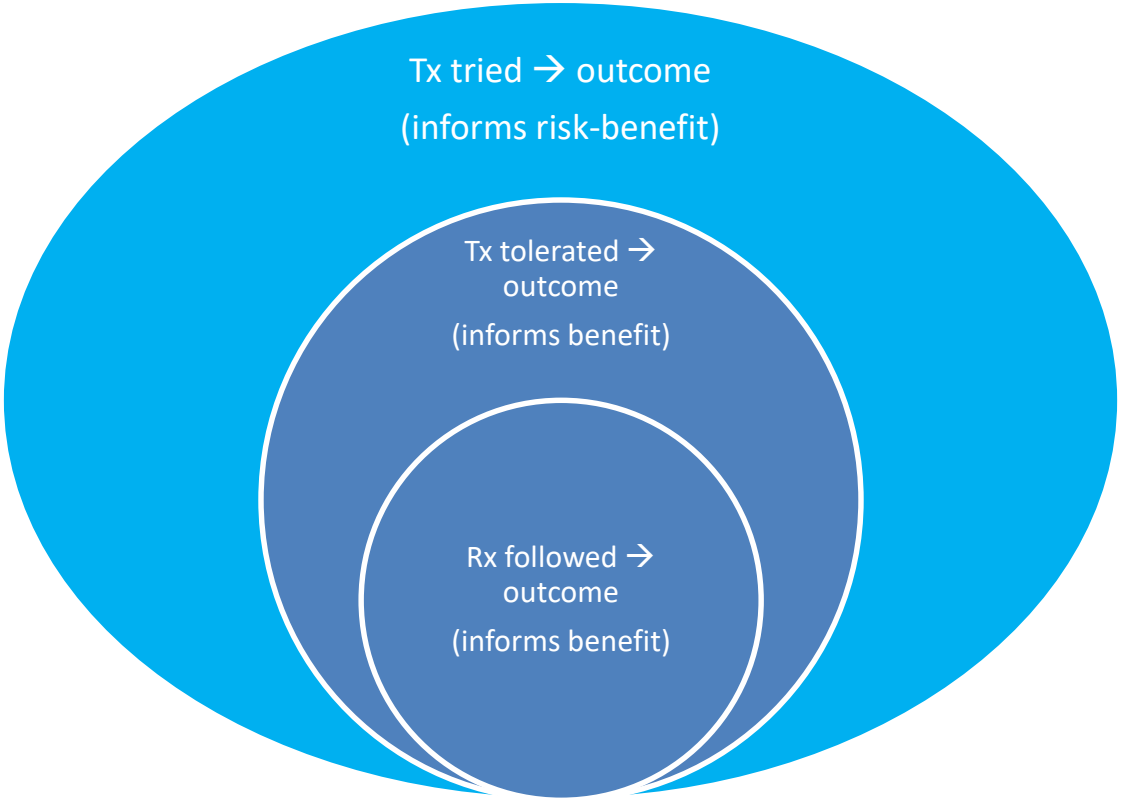
(a) The purpose … is to distinguish the effect of a drug from other influences…

CFR §314.125 Refusal to approve

(5) **There is a lack of substantial evidence …that the drug product will have the effect …under the conditions of use prescribed, recommended, or suggested in its proposed labeling.**

(3) **…the drug is unsafe for use under the conditions prescribed….**

Focusing in Further: The ‘Medicine level’



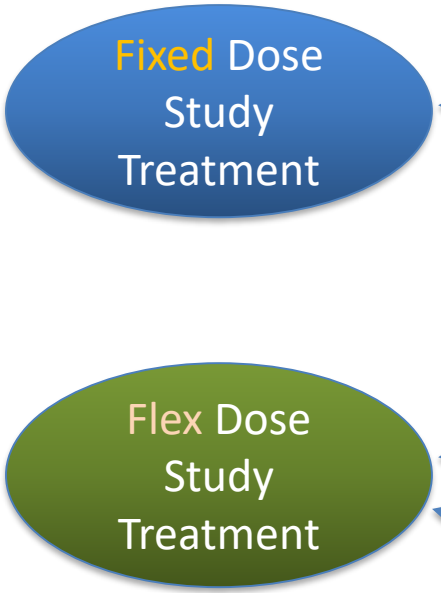
Consider all estimand components

3. Define population of interest

- e.g., patients with an acute moderate to severe episode of MDD

4. Select study treatment/ treatment algorithm

Regulatory decisions can inform study treatments



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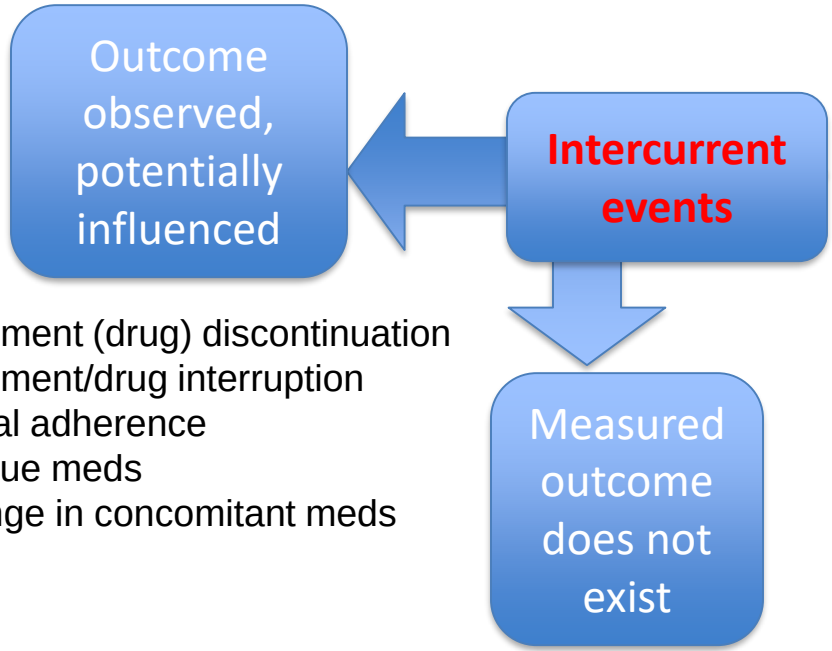
5. Define intercurrent event strategies



Sources of missingness (outcome not observed – not intercurrent events)

- Treatment (drug) discontinuation
- Treatment/drug interruption
- Partial adherence
- Rescue meds
- Change in concomitant meds

- Events leading to study withdrawal (drop-out)
  - Unrelated
  - TEAEs
- Missed data measurements

- Death/Coma
  - Indication-related
  - Indication-unrelated

Most common intercurrent event strategies

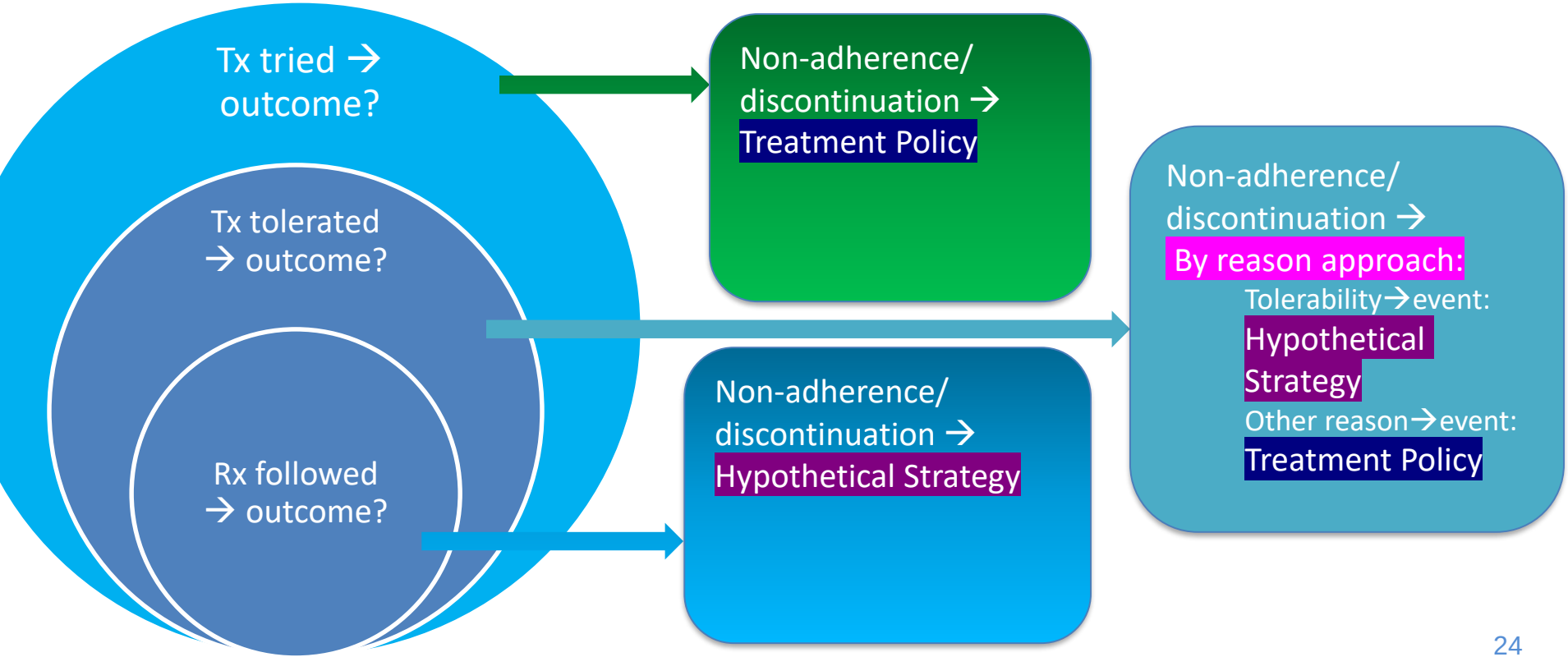
- **Treatment policy strategy**

"The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs."

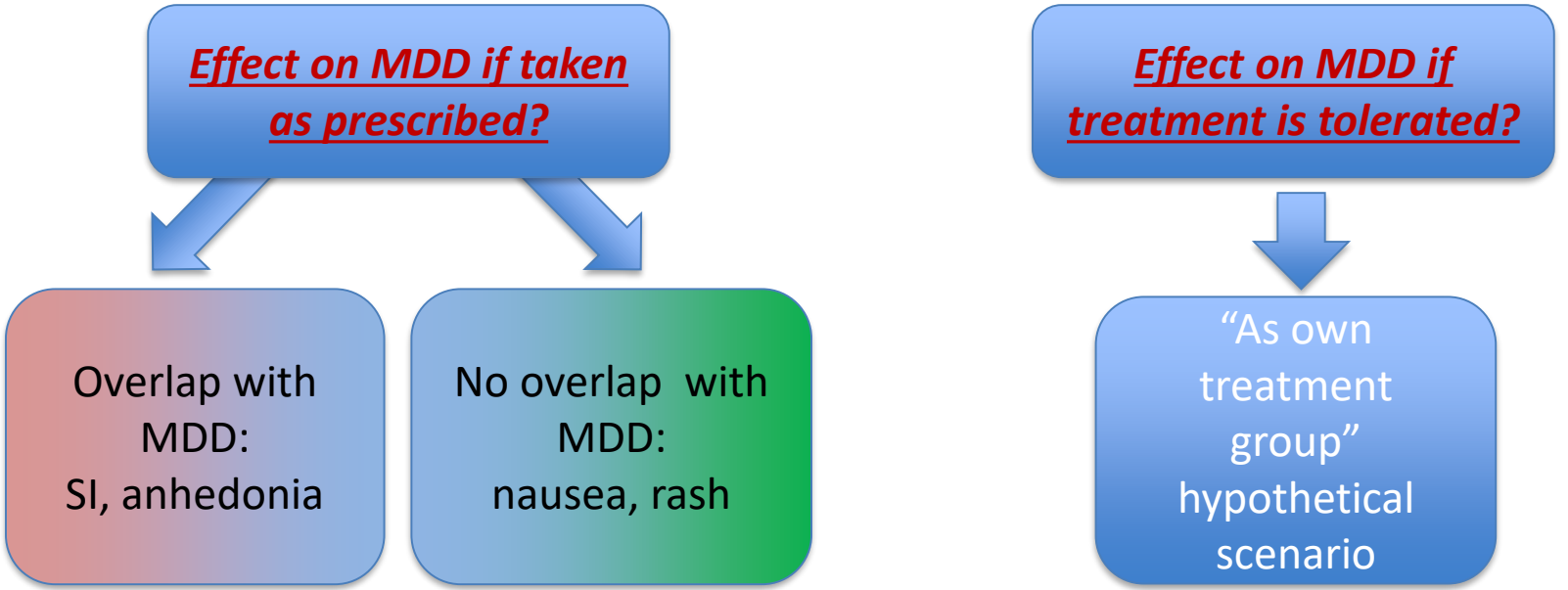
- **Hypothetical strategies**

"A scenario is envisaged in which the intercurrent event would not occur: the value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined."

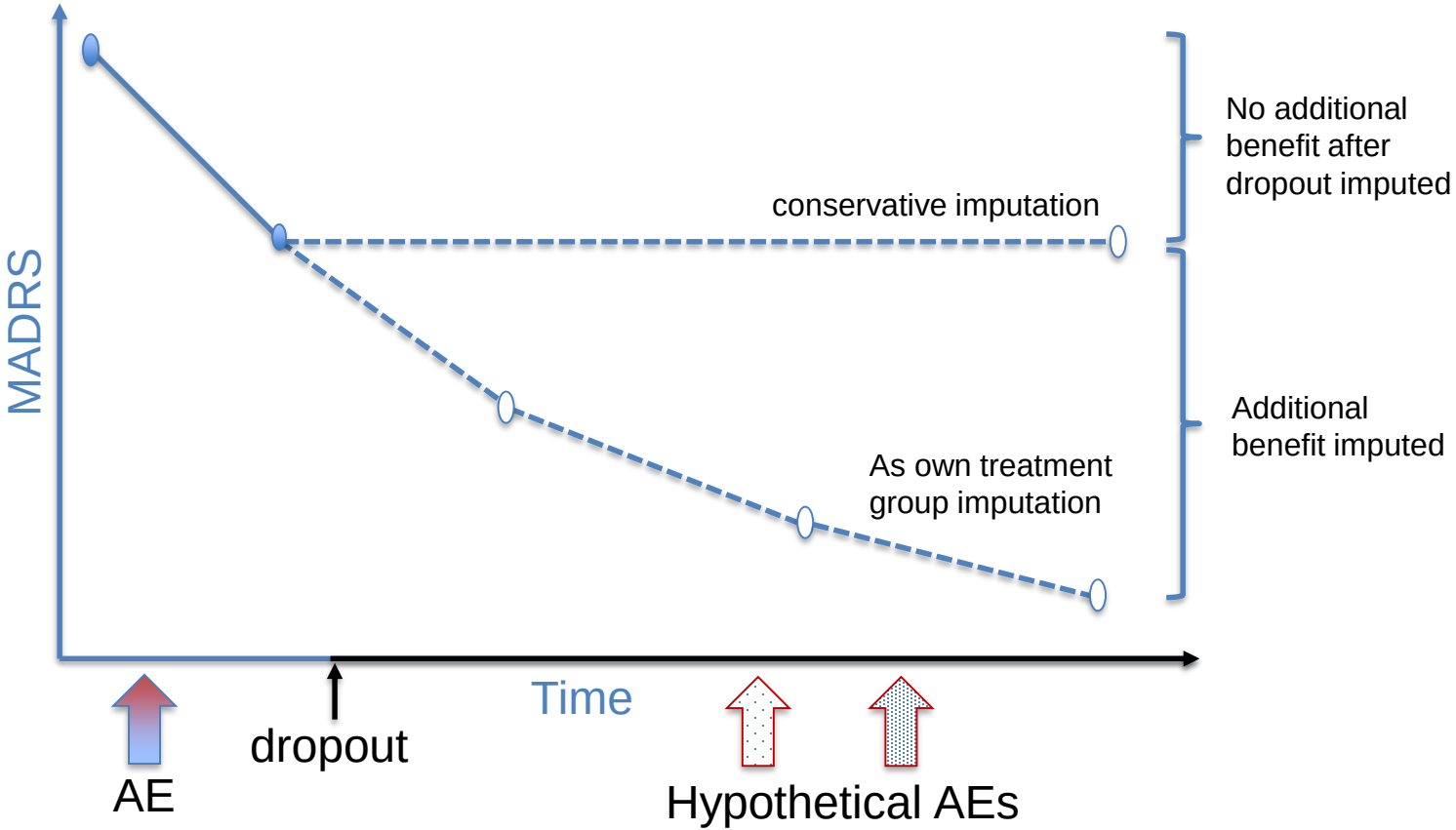
What intercurrent event strategy to use for a given efficacy framing question?



What missing data strategy to use for a given efficacy framing question? *Case: TEAE→dropout*



Imputation of missing data: Implications for Risk-benefit vs. Benefit-only analysis



Conclusions

- Estimands make the treatment effect we are estimating explicit and should inform trial design
- Practical concerns may constrain what we are able to estimate, requiring revision of the estimand
- Such constraints also depend on the target disorder
- Estimands may therefore be disorder-specific
- Different estimands may be needed to address different regulatory issues

Questions?

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