# Challenges of Safety and Dual Benefit-Risk Estimands

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Inspired by patients.
Driven by science.

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# Overview

- Overview of Estimands
- Safety Estimands & Challenges
- Benefit-Risk Estimands & Challenges
- Diabetes Example
- Concluding Remarks

# Overview: Components of an Estimand

- **Targeted population**

  defined by the inclusion and exclusion criteria of the study.

- **Endpoint**

  variable

- **Intercurrent events**

  a post-randomization intervention effect that potentially influences the endpoint

- **Summary measure**

  summarizes the comparison of the two treatments under investigation.

# Safety Estimand Statement

**For patients exposed to the drug (*target pop*),**

**is the clinical outcome (*variable*),**

**summarized by a method that best characterizes**

**the event (*summary measure*),**

**higher than expected,**

**considering post-randomization events (*intercurrent events*)?**

## Safety Estimand Statement

For patients exposed to the drug *(target pop)*,

is the clinical outcome *(variable)*,

summarized by a method that best characterizes the event *(summary measure)*, *higher than expected*,

considering post-randomization events *(intercurrent events)*?

## Benefit-Risk Estimand Statement

For patients exposed to the drug *(target pop)*,

are the *trade-offs* positive between the benefits & risks *(variables)*,

when summarized by methods that best characterize them *(summary measures)*, and

considering post-randomization events (*intercurrent events*)?

# Challenges of Safety Data

- **Endpoint**
  - Multi-faceted: Severity, Duration , Reversibility, Unequal weights, Competing events
  - Follow-up time often too short or unequal between treatments
  - AEs are often retrospectively defined
  - Independent adjudication often required
  - Components of composite AEs  (ex. MACE) are unequally weighted
- **Intercurrent Event**
  - Mechanism of missingness uncertain
  - Imputing missing values impossible/challenging
- **Summary Measure**
  - Different AEs require different metrics
- **Other**
  - Treatment relatedness uncertain
  - Different study designs make meta-analysis difficult.

# Asymmetry of assessing benefits and risks

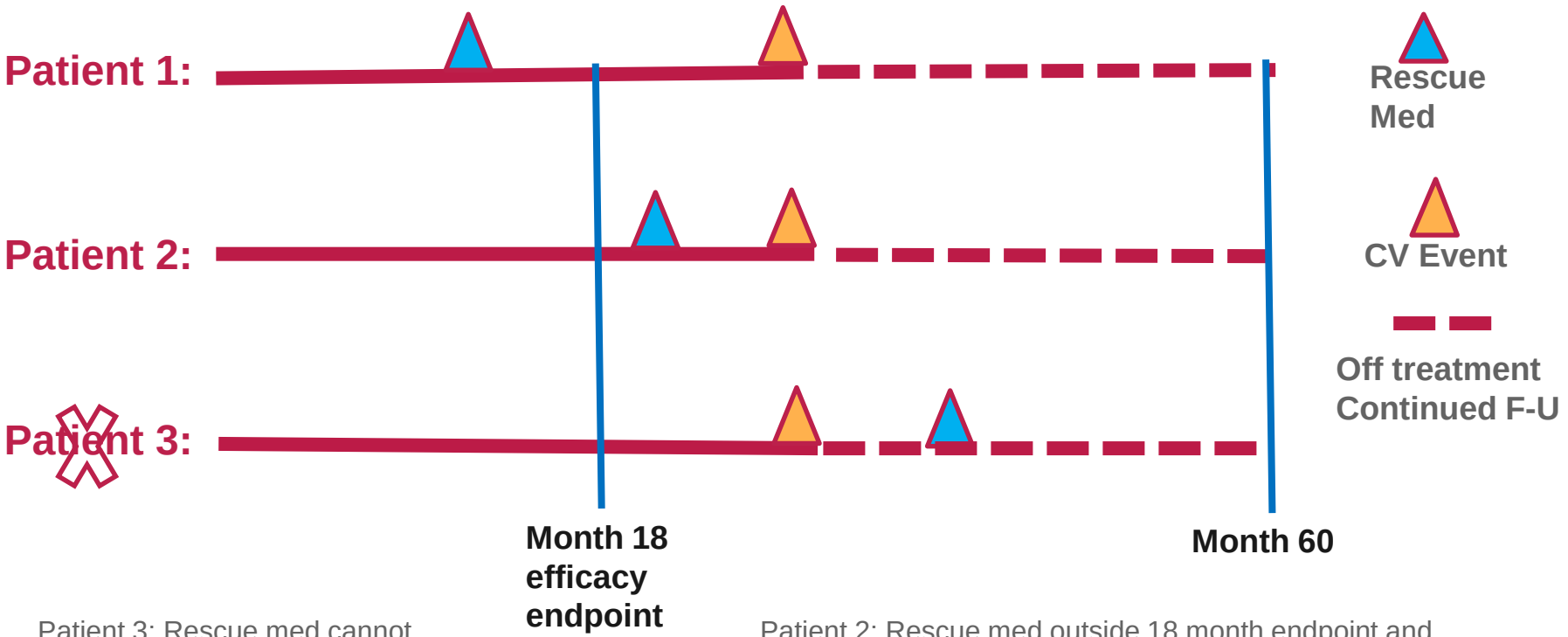
- Efficacy is typically primary & powered, while safety is exploratory.
- Safety outcomes are often unexpected, unanticipated, or confounded with the disease.
- Inclusion/Exclusion criteria are more likely to exclude patients at highest risk.
- AEs have a different event ascertainment, adjucation & follow-up.
- Limited no. of efficacy endpoints and unknown number of safety endpoints.
- Scales may differ in capturing time dependency.
- Weighting multiple benefits and risks is difficult.
- Combining benefits and risks in a single endpoint is difficult.

**Ref. O'Neill RT. A perspective on characterizing benefits and risks. Derived from clinical trials: can we do more?.** Drug Information Journal 2008; 42:235–245.

# Example: Diabetes Long-term Safety Study

| | Benefit | Risk |
|---|---|---|
| Question | Can study drug better control HbA1c than standard of care? | Does the study drug have an increased cardiovascular risk? |
| Intercurrent Event | Rescue add-on therapy For lack of efficacy | ? |
| Estimand | ? | ? |
| Variable | HbA1c by month 18 | Time to CV death or CV related hospitalization by month 60 |
| Metric | Difference in means | Hazard ratio |
| Population | High risk patients who need additional glycemic control. Inclusion/exclusion criteria resemble real world. | |

# Relationship between rescue med and CV event




Patient 3: Rescue med cannot be observed after CV event

Patient 2: Rescue med outside 18 month endpoint and possibly extend F-U to CV event

# How add-on rescue med is viewed

**Treatment policy (ITT): Occurrence of intercurrent event ignored**

**Patients are still taking the assigned treatments after the rescue med is added on.**

**Following the ITT Principal, so it is inconsequential, *i.e. not a treatment failure.***

**Answers question of what to expect if study drug is prescribed in the clinic over an extended period of time.**

**While on treatment: Response to treatment prior to the occurrence of the intercurrent event is of interest.**

**The rescue medication *marks the end of study treatment*. Only data before the rescue medication will be analyzed.**

**Answers question of which is better treatment when given alone, with no regard to months 18 & 60 follow-up.**

# How add-on rescue med is viewed

**Composite: Intercurrent event is component of variable**

**Made part of the variable definition of *treatment failure* along with uncontrolled HbA1c.**

**Answers question of which assigned treatment simultaneously better controls HbA1c and does not need rescue.**

**There is high overlap between patients with poor control and with rescue med anyway.**

**Principal stratum: Target population is subpopulation for which intercurrent event would not occur**

**Interest is only in comparing the original treatment assignments. Patients with rescue med are *not included* in the target population.**

**Answers question of which is a better treatment in patients not receiving rescue.**

# How add-on rescue med is viewed

**Hypothetical: Scenario is envisaged in which the intercurrent event would not occur**

**An algorithm will derive an HbA1c value expected after rescue med, as if the *rescue med was not available*. Not sure if this has ever been used for a safety endpoint.**

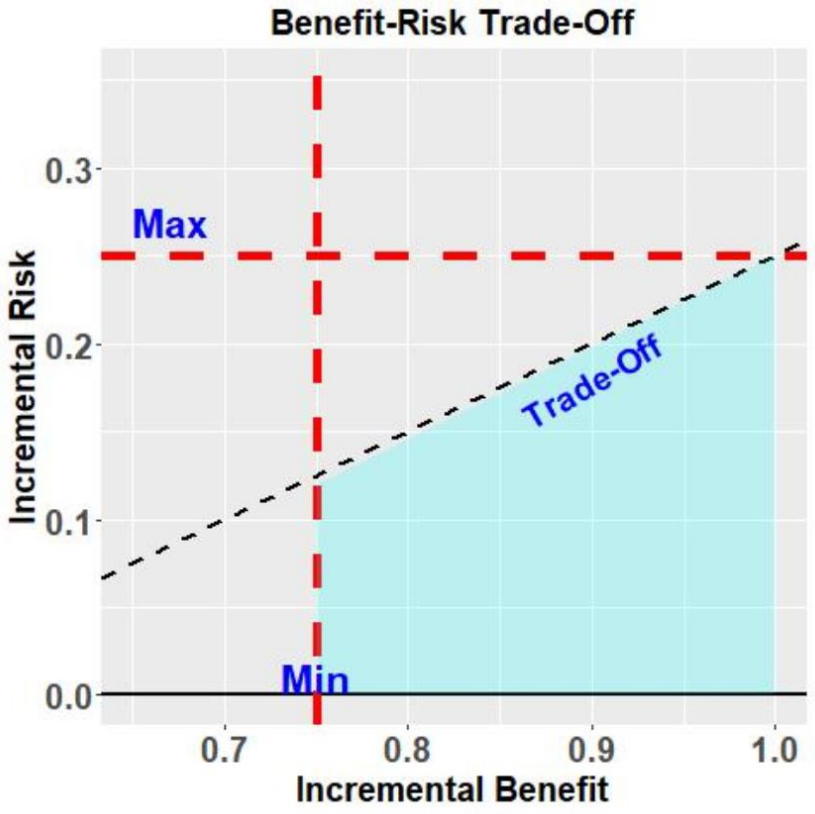
**Answers question of which is better treatment in the absence of a rescue med.**

# Effect of Add-on Rescue Meds on Endpoints

## Change in HbA1c by month 18 and CV risk by month 60

| Estimand | Effect | Benefit | Risk |
|---|---|---|---|
| **Treatment Policy** (not considered) | Effect due to either assigned or add-on rescue med. | Higher chance of controlling HbA1c | Full follow-up -> Better capture |
| **Composite** (variable) | Drug needing less rescue has better efficacy | Lowers chance of reaching endpoint | 60 month follow-up unaltered |
| **While on Treatment** (variable) | Endpoints no longer 18 & 60 month outcomes | Not evaluable | Not evaluable |
| **Principal Stratum** (population) | No rescued patients | Narrow range of change | Fewer patient: lower rare event rate. |
| **Hypothetical** (modeled) | Rescue data replaced by imputations | Effect due to assigned med. | Many assumptions to be met. |

# Benefit-Risk Trade-Offs – the last challenge

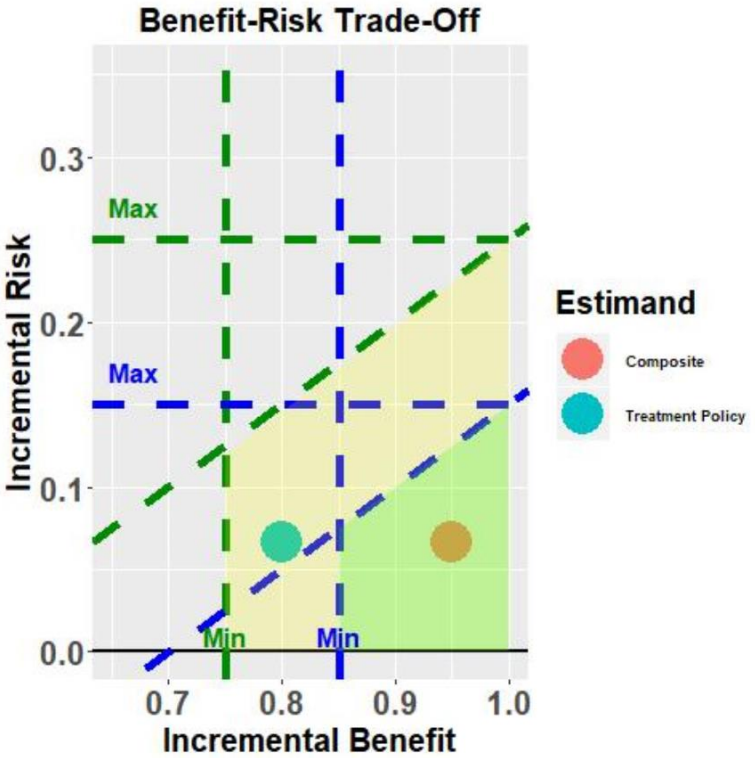



**Decision makers compare the study adverse event rate to a *maximum acceptable risk (MAR)* and compare the study efficacy to a *minimum acceptable benefit* (MAB).**

**When comparing them simultaneously, they assess each level of benefit for a given level of risk. As the risk increases, so must the benefit.**

**This relationship is the *benefit-risk trade-off curve*.**

# Estimands & Benefit-Risk Trade-Offs




**The choice of estimand will have an impact on its respective MAR, MAB and Benefit-Risk Trade-off.**

**In this example, an estimand such as a Composite, might have a smaller acceptance region (green) than another estimand, such as Treatment Policy (yellow).**

**These thresholds are how medical judgement is combined with clinical data to make decisions.**

# Key Q&A

**Do the intercurrent events effect efficacy and safety differently?**
Most likely, depending on whether they are considered treatment failures and alter the length of follow-up needed to assess safety.

**Should the same type of estimand be used for benefits and risks?**
Not necessarily. The estimands should match the study objectives.

**What is to be gained by assessing benefits and risks together?**
A benefit and a risk can separately meet their acceptable criteria but together fall outside an acceptable trade-off. Ultimately, decision makers must assess this trade-off either formally or informally.

**Is it possible to have a single estimand for benefit-risk?**
Two approaches are (1) Multi-Criteria Decision Analysis, which assigns weights or utilities to each benefit and risk, and (2) defining health states that are composites of benefits & risks (ex. composite estimand of HbA1c<7 w/o CV event). Acceptances of these approaches depends on the stakeholder / decision maker.

# Questions?

# Thanks!