# A Case Study of Hypothetical Strategies in Acute Pain

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# Disclaimer

- This research was conducted by the authors when they worked at FDA.
- This presentation reflects the personal views of the authors and should not be construed to present FDA, Otsuka or AstraZeneca.

# Outline

- Concerns on hypothetical strategies
- Introduction to acute pain
- Hypothetical strategy to handle rescue use in acute pain
  - Clinical and regulatory relevance of the clinical question of interest
  - Assumptions needed to construct the estimator
  - Ways to deal with uncertainties from assumptions
- Summary

# Concerns on Hypothetical Strategies

- Clinical questions: Is it of clinical and regulatory interest?
- Estimation: Is there a reasonable estimator that does not rely on strong assumptions?

We will address all these concerns in this case study.

# Acute Pain

- Population: post-surgery patients. Usually in hospital setting. As the effects of anesthesia medicines ⇘, pain intensity (PI) ⇗.
- Trial duration
  - Reflects the expected duration of pain for the specific surgery.
  - Ranges from 12 to 96 hours.
- Pain is more severe at the beginning.
  - Frequent PI measurements at the beginning.
- Rescue medications are pre-specified in protocols

# Choice of Efficacy Outcomes in Acute Pain

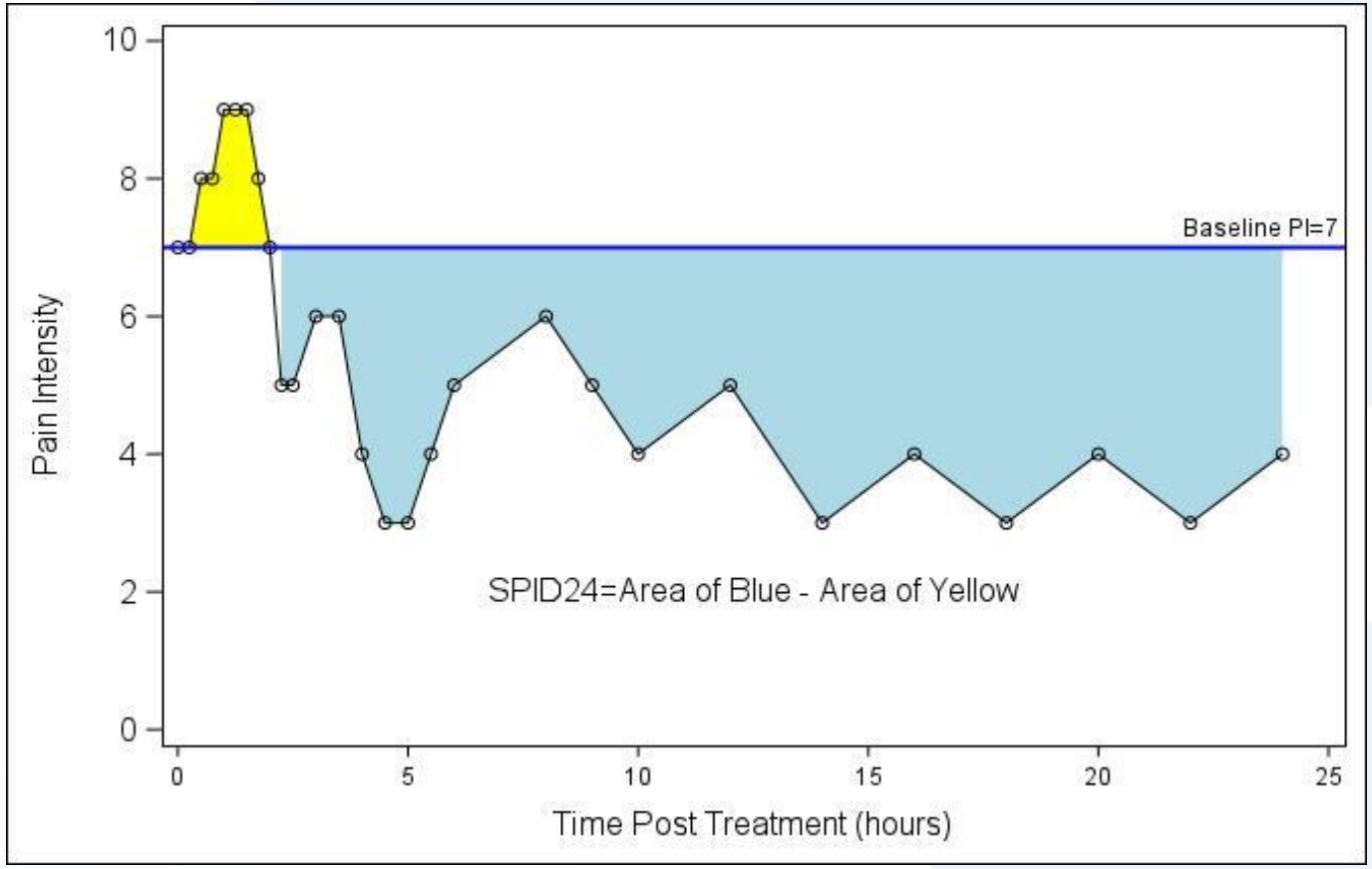
FDA draft Guidance 2022: Development of Non-Opioid Analgesics for Acute Pain

- Primary outcome measure needs to be assessment of pain intensity.
- Many secondary endpoints are rescue related:
  - time to first rescue use, time to first opioid rescue use, percentage of patients used rescue, percentage patients used opioid rescue, amount of rescue use, amount of opioid rescue use, etc.
- Endpoint associated with eliminating or reducing opioid use may be supportive of efficacy.

# Primary Endpoint for Acute Pain

Summed Pain Intensity Differences from Baseline (SPID)

- A measurement of cumulative pain reduction over the trial duration
- SPID goes the opposite direction of PI



# Most Impactful Intercurrent Event in Acute Pain: Rescue Medication Use

- Due to ethical reasons, both arms need:
  - Adequate pain relief
  - Extensive use of rescue medication, including non-protocol rescue medication and opioids
- Unbalanced occurrence between arms: Placebo arms are expected to have more and earlier rescue.
- PI measured prior to every rescue use

# Example: Anjeso (Intravenous Meloxican)

- Two positive trials: one bony surgical model (bunionectomy), one soft tissue surgical model (abdominoplasty)
- Pre-specified rescue medication: oral oxycodone 5 mg
- Percentage of patients that used rescue was extensive[1]

| Study | Placebo | Anjeso |
|---|---|---|
| 1 | 91% | 88% |
| 2 | 98% | 83% |

Placebo arm is essentially an oxycodone arm

1: statistical review at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210583Orig1s000StatR.pdf

# Clinical Question of Interest

- What is the cumulative pain reduction attributable to treatment alone compared with placebo alone?

This question is equivalent to:

- What would be the cumulative pain reduction from treatment compared with placebo if rescue drugs were not available? Hypothetical estimand.

Treatment policy: what is the cumulative pain reduction attributable to treatment and rescue together even if the rescue medication usage is not balanced?

Hypothetical strategy is more clinically relevant than treatment policy.

<u>This clinical questions is of clinical interest.</u>

# ICH E9 R1 Acknowledge the Potential Importance of Treatment Effect if Rescue Medication not Available

- Page 7, line 14 from the bottom

"*Specifically, when additional medication must be made available for ethical reasons, a* ***treatment effect of interest might concern the outcomes if the additional medication was not available****"*

- Page 11, line 5 from the bottom

*"The question of what the values for the variable of interest would have been* ***if rescue medication had not been available may be an important one****."*

# The Clinical Question is of Regulatory Interest

- FDA guidance May 2020:  Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework Guidance for Industry
  - “Superiority to other available treatment is not a requirement for approval”
  - More rigorous benefit and risk assessment for opioid analgesic drugs: both treatment effect size and safety signals are compared to those available treatments.
  - FDA is encouraging the development of non-opioid analgesic by providing expedited review programs.
- For an accurate risk and benefit assessment, it is important to know the treatment effect of the investigational drug in the absence of rescue medication.
- Without adjusting for use of rescue medication, it is almost impossible to approve non-opioid analgesic medicine for acute pain because some placebo arms are essentially opioid arms.

# Assumptions used for Estimation

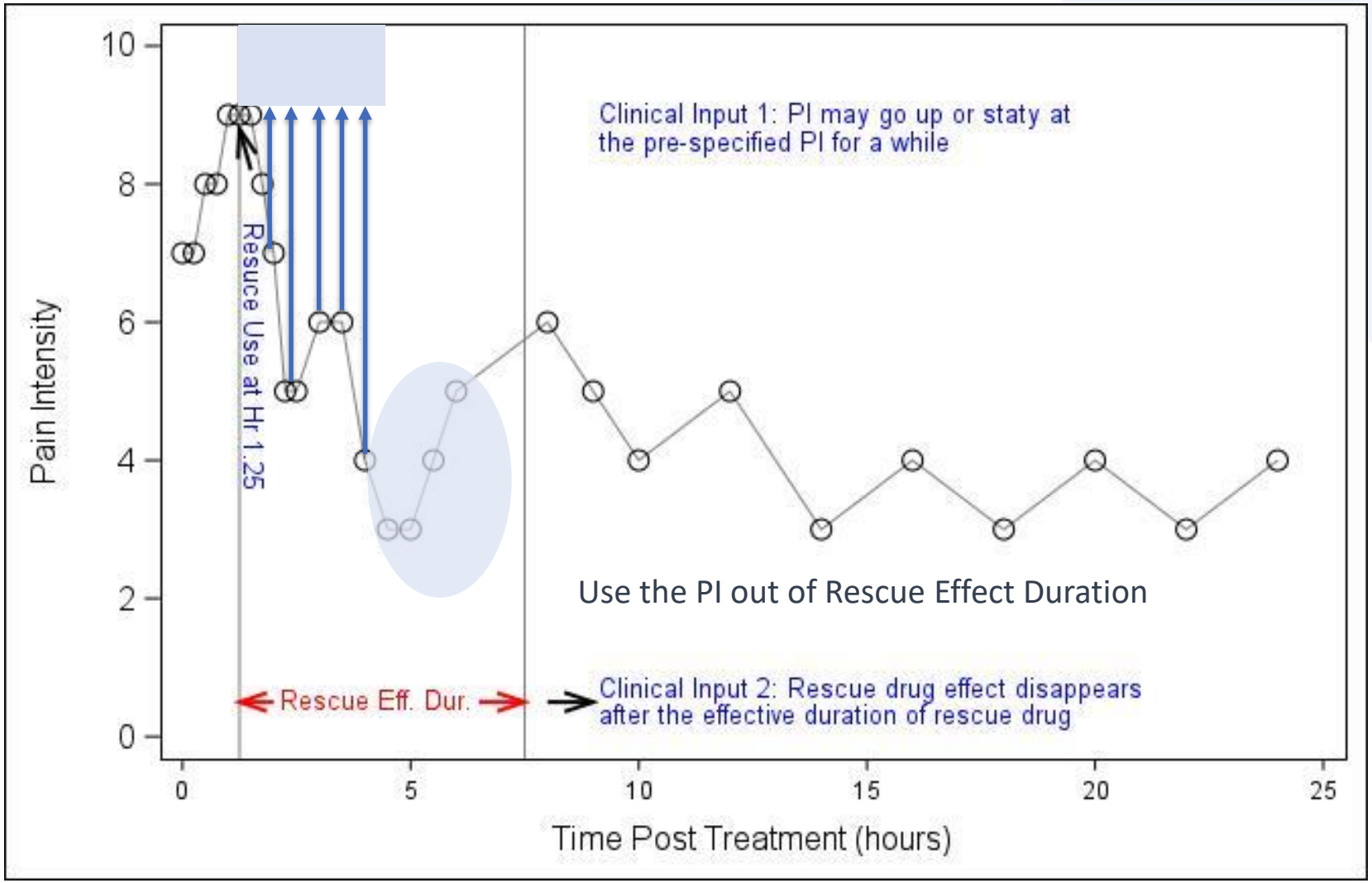
Question: What PI would patient have if rescue medication had not been available ?

Clinical inputs:

1. Pain intensity may go up or stay at the pre-rescue pain score for a while.
2. The pain relief from the rescue medication completely disappears after the effective duration of the rescue drug.

These are widely-accepted and non-controversial statements.

# Converting Clinical Inputs into Patients Pain Curves

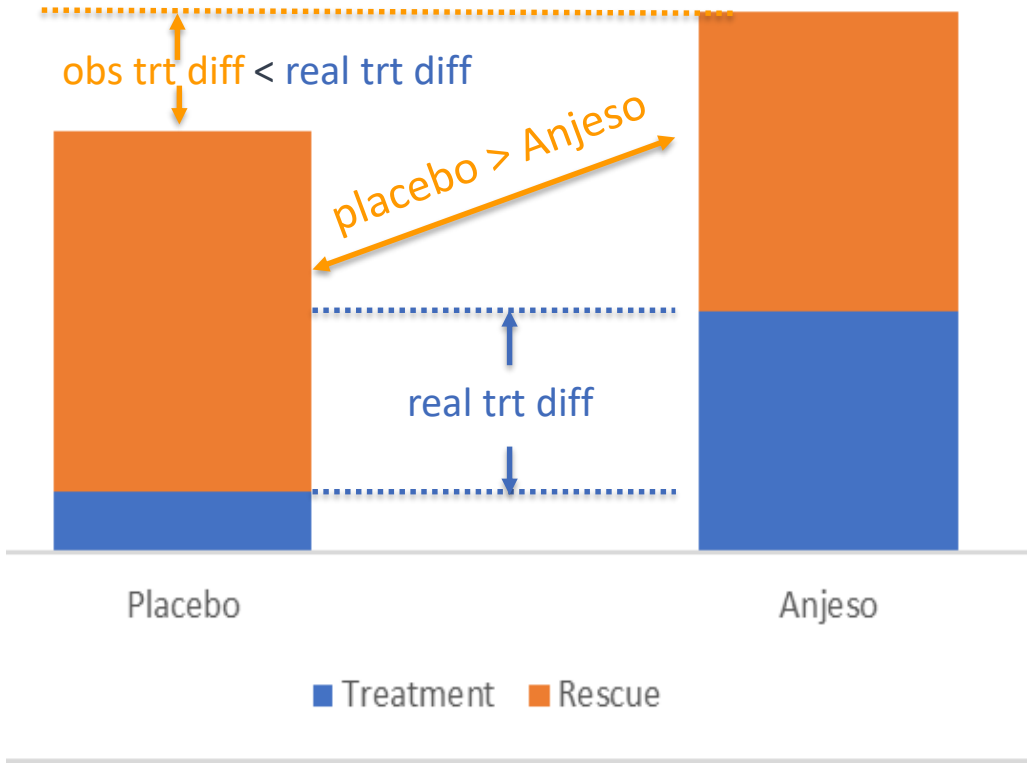



Uncertainties:

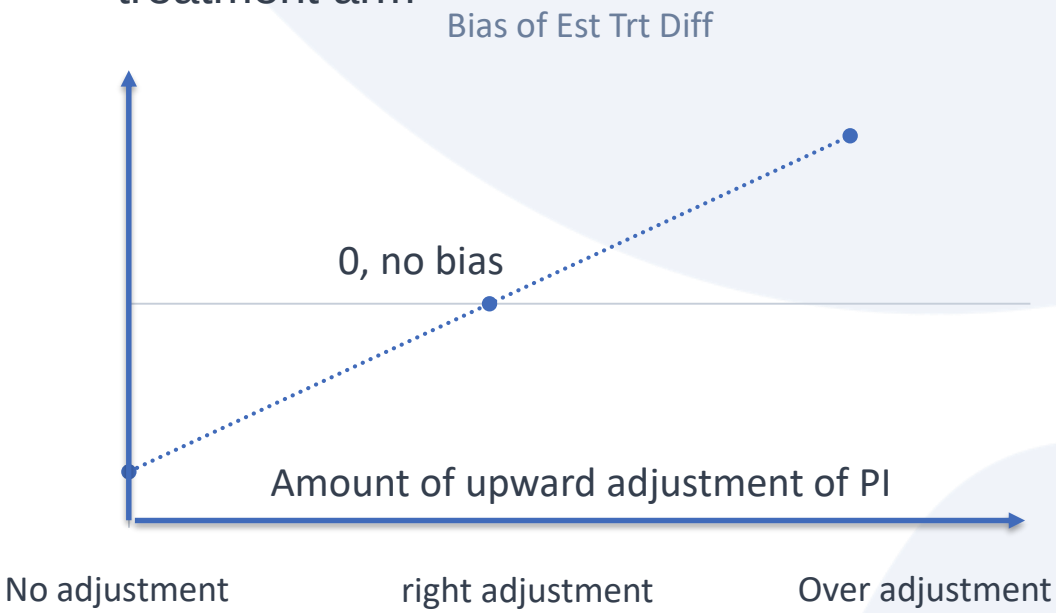
- The width of the blue box >0
- The imputed PIs in the blue box
- The imputed PIs in the blue oval

# How to Deal with Uncertainties in a Conservative Way?

## Observed Cumulative Pain Reduction

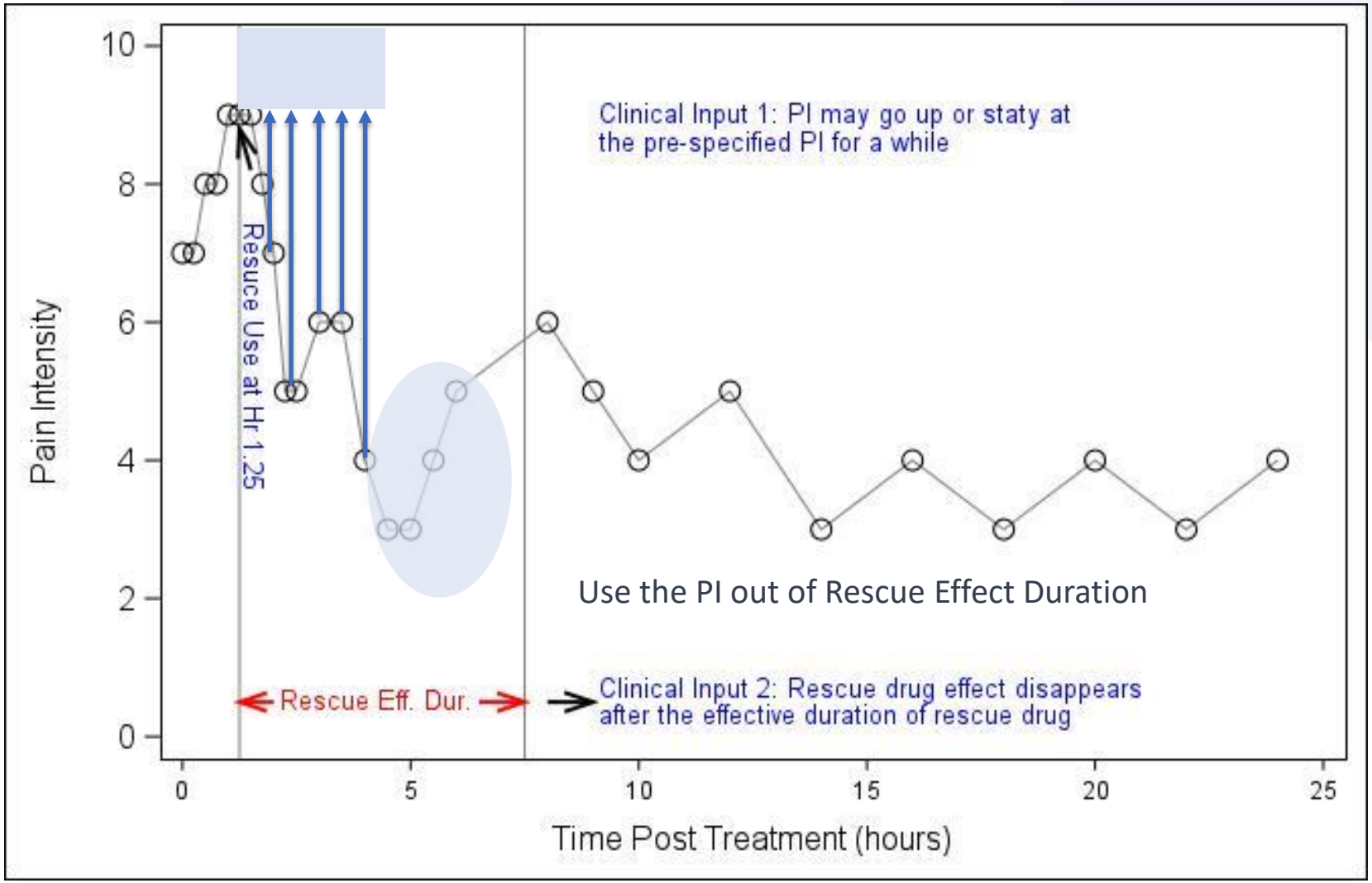



A requirement for acute indication: More patients in placebo arm use rescue than treatment arm




The less upward adjustment of PI, the more conservative of estimated treatment difference

# Dealing with Uncertainties in Estimation




Uncertainties:

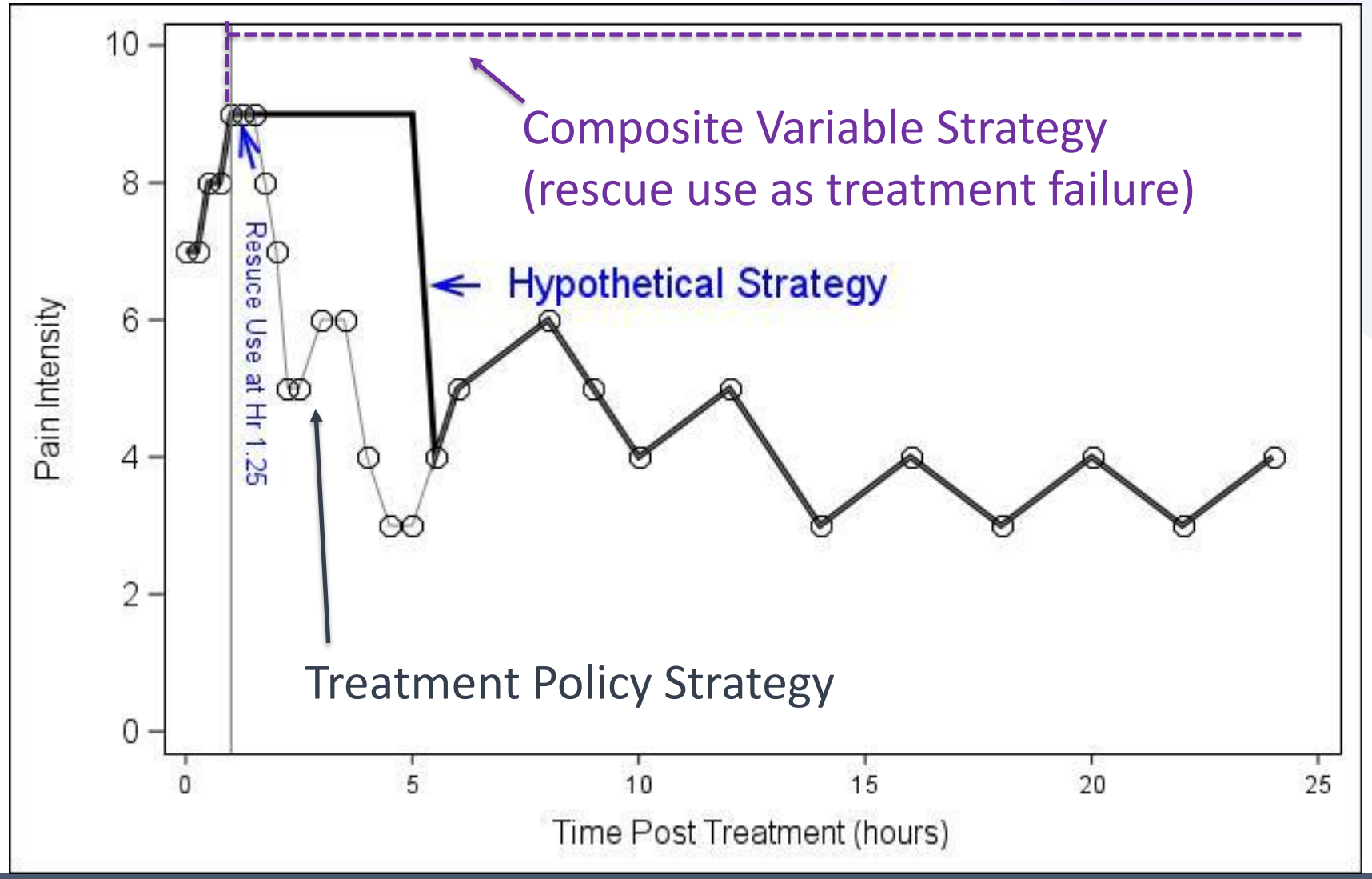
- The width of the blue box >0, x hours
- The imputed PIs in the blue box **Pre-rescue PI**
- The imputed PIs in the blue oval **No Change**

**The uncertainty of x:**

Primary analysis: pre-specified $x_0$, usually the half life of the specific rescue drug.

Sensitivity analysis: vary x

# The Primary Analysis




Primary Analysis: Multiple imputation carries pre-rescue PI for $x_0$ hours

Sensitivity Analysis: vary x

When x -> 0, no PI will be replaced. It is the treatment policy strategy

When x = 24 hours and use the worst possible score, it becomes the composite variable strategy

# A Reasonable Estimator without Strong Assumptions

Two concerns about estimation of hypothetical strategies:

- strong assumptions

The primary analysis method is based on two clinical inputs which are widely accepted and non-controversial. No Strong Assumptions.

- Is it a reasonable estimator?

It does not rely on strong assumptions. It is conservative whenever there are uncertainties in clinical inputs or have sensitivity analysis to deal with uncertainties. The estimator is a reasonable estimator for decision making.

# Summary of the Case Study

We have demonstrated:

- The clinical questions “What is the accumulative pain reduction attributable to treatment alone compared to placebo alone?” is of clinical and regulatory interest.
- There is a reasonable estimator for decision making
  - No strong assumptions
  - Sensitivity analysis and conservatism are used to address uncertainties in clinical inputs.

The Hypothetical strategy is reasonable to handle rescue use in acute pain trials.

Remaining concerns about this estimand: the word “hypothetical”.

There should be a rightful place for this reasonable estimand in the estimand family. How about “treatment attributable” estimand?

# Acknowledgements


- James Travis for his discussion of estimands in his statistical review of the first-round submission of Oliceridine.
- FDA CDER estimand working group, especially, James HM Hung, Lei Nie, and Shanti Gomatam.
- Division of Anesthesiology, Addiction Medication, and Pain Medicine (DAAP), Office of Neuroscience, FDA