# Efficient, doubly robust estimation of the effect of dose switching for switchers in a randomised clinical trial

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joint work with Stijn Vansteelandt and An Vandebosch

janssen

# Background

- Phase 3 program of a new experimental compound for patients with a chronic condition
- Consisted of multiple studies, including

**FIXED DOSING TRIAL ($T = 0$)**

HIGH DOSE ($D = h$)

LOW DOSE ($D = l$)

(FIXED) PLACEBO

**FLEXIBLE DOSING TRIAL ($T = 1$)**

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- Examples: **neuroscience** (e.g. Invega, Spravato, . . . )
- Why?
  - Need 2 positive efficacy trials for approval
  - Fixed: dose-response for efficacy evaluation
  - Flexible: presumed dosing strategy in clinical practice

# Study Results

- Protocols are similar in
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## Research Question

*Is* **flexible dosing potentially beneficial** *(in terms of treatment effect* **compared to the low dose***) for* **switchers** *in the treatment arm of the flexible dosing study?*

# Problem Setting

**FLEXIBLE DOSING TRIAL ($T = 1$)**

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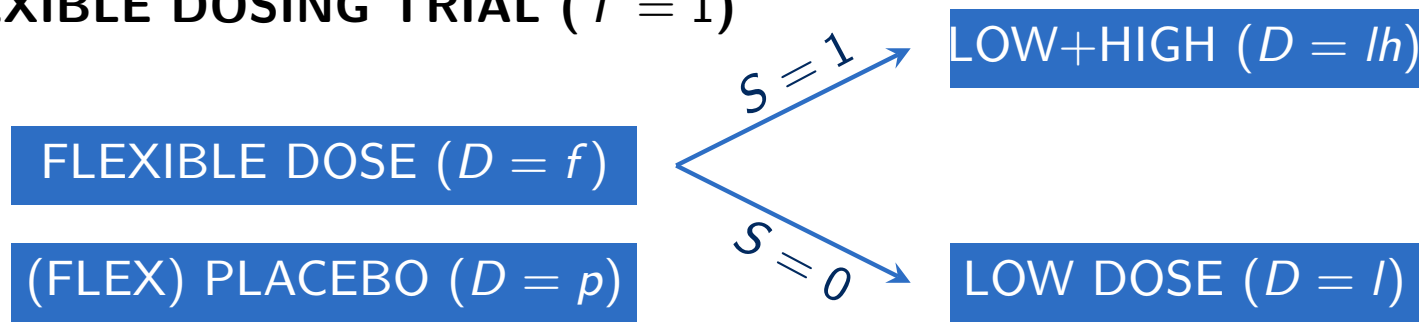

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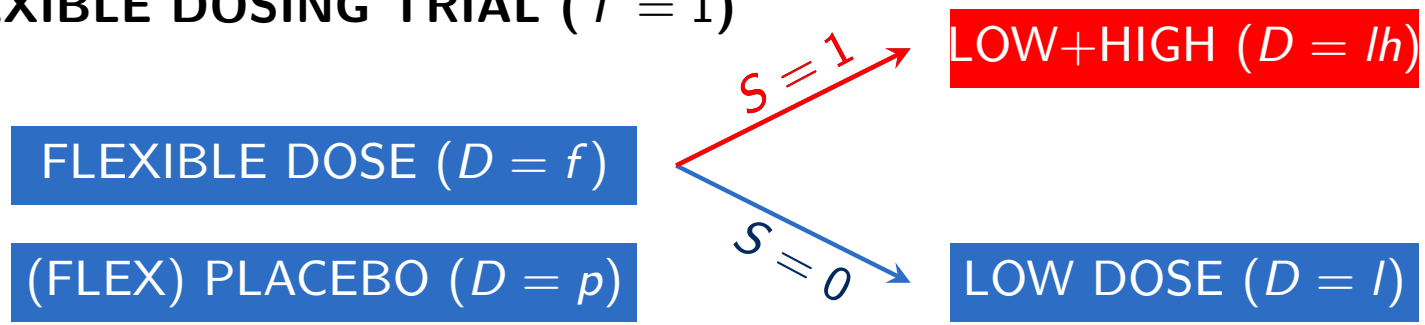

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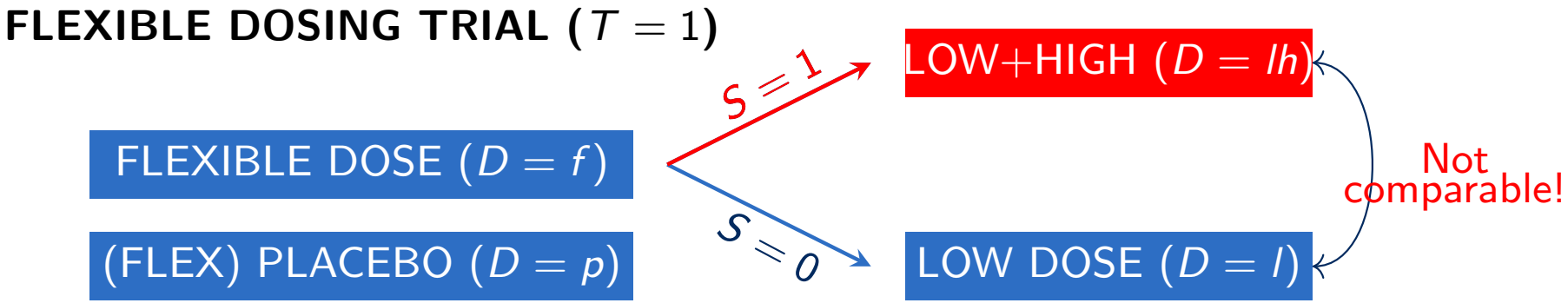


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  - e.g., latter patients usually in a better health condition

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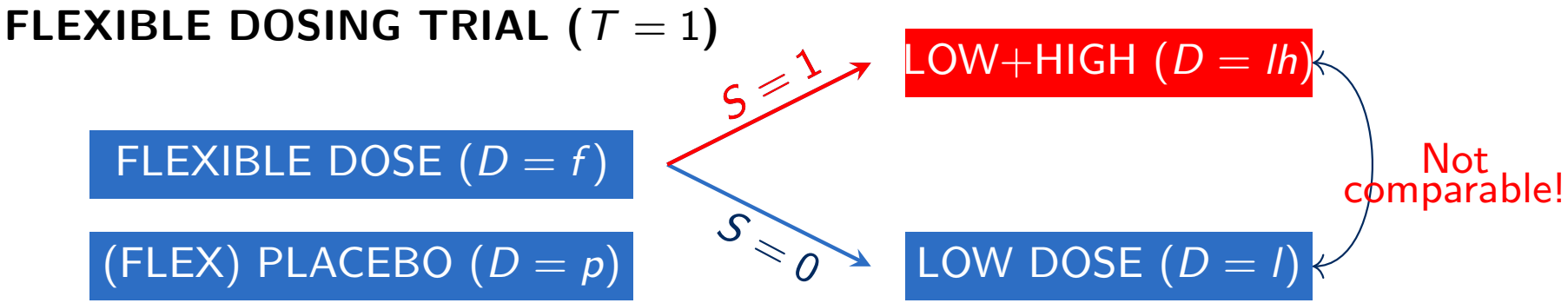


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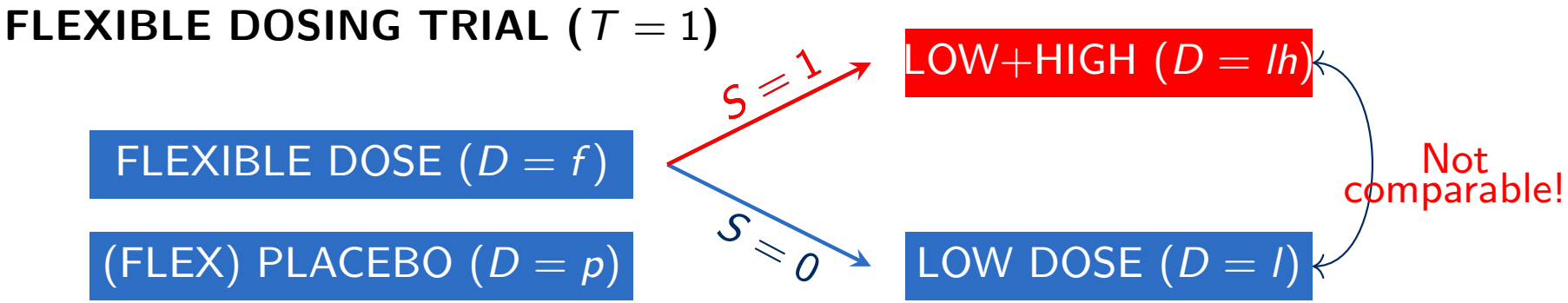


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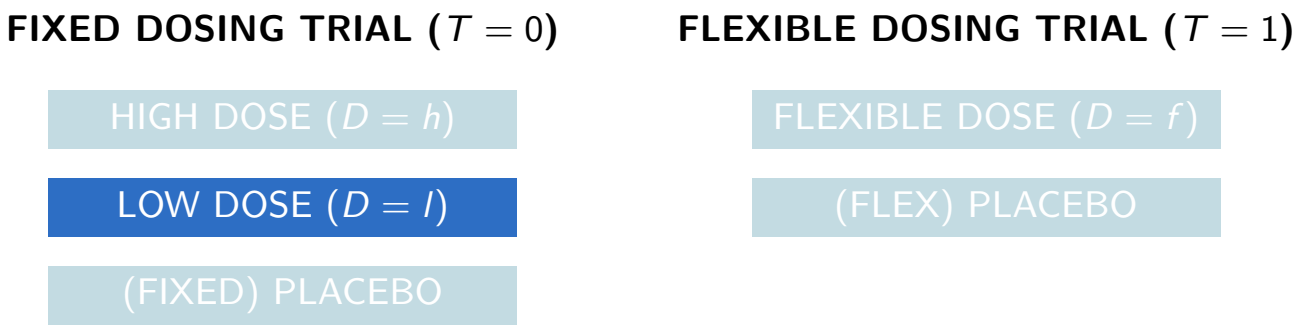
- Available information too scarce: no arm assigned to fixed low dose

# Problem Setting: Possible Solution

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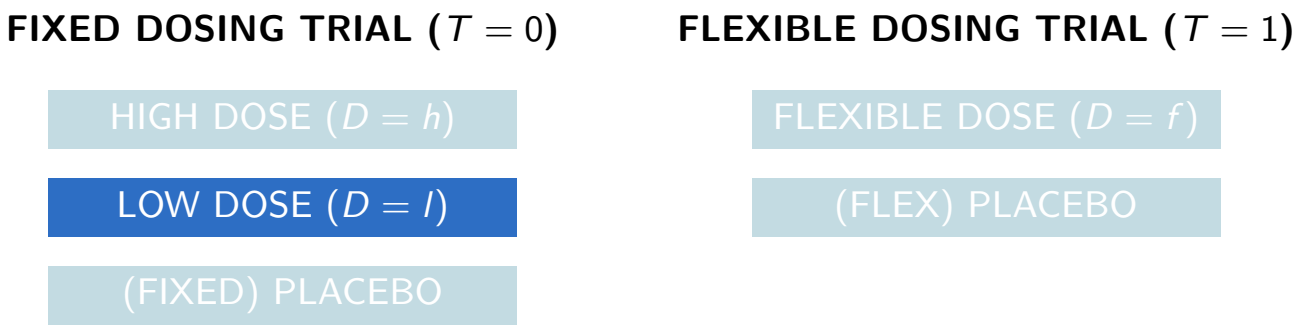


- Possible Solution
  - Can we employ data from the fixed dosing trial (i.e., low dose)?
  - Possibly correcting for imbalances between trials?
- Transport data from low dose arm of fixed dosing trial
  - using similar techniques as for transporting inferences from trial participants to new target population

# Question Formalized - Estimand

## Goal

*In flexible dosing study, for those who required switching:*

*How different would the average response $Y$ have been for them, had they not switched:*

$$E[Y^{lh} - Y^{l} | T = 1, D = f, S = 1]$$

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$\Downarrow$ Some calculations

$$E[Y^{\mathrm{f}} - Y^{l} | T = 1, D = f] / P(S = 1 | T = 1, D = f)$$

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- Note: expectation is an ATT effect!

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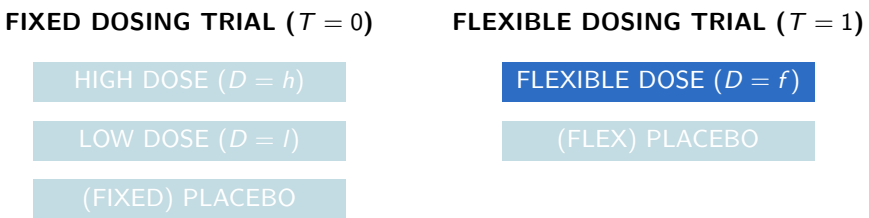


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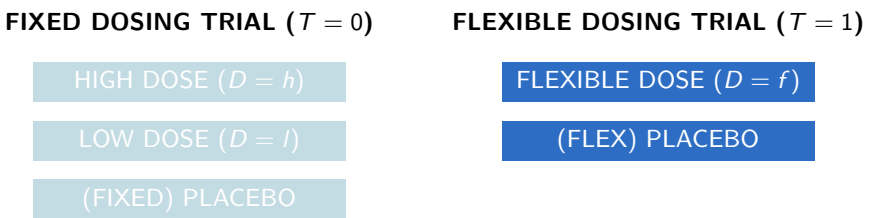


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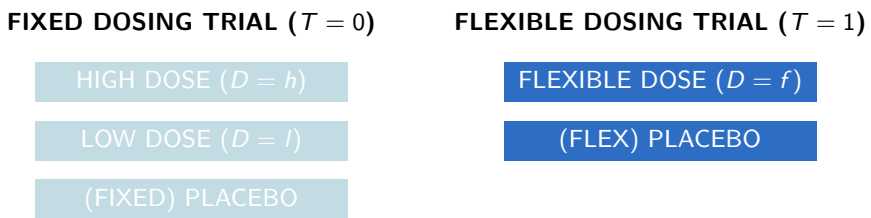


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1. Fitting a regression model for $Y$ given baseline covariates $\boldsymbol{X}$ among the patients on the flexible dose.
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3. Taking the average of the predicted values over all patients in flexible dosing trial.

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- Cannot be directly estimated from flexible dosing trial

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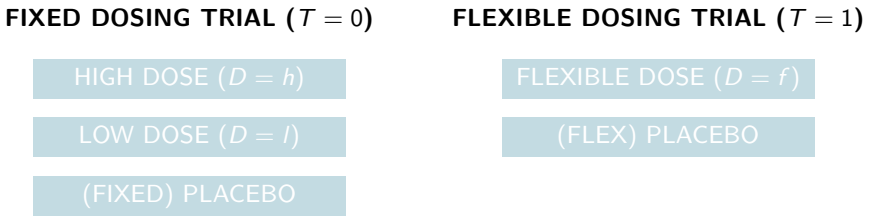


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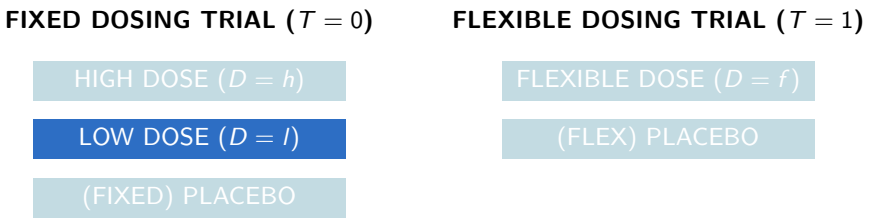


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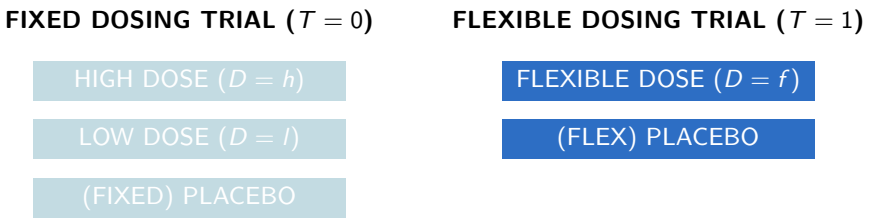


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3. Taking the average of the predicted values over all patients in flexible dosing trial.

(Shu and Tan, 2018)

# Proposed Estimator

- This semi-parametric estimator, relies on
  - Selection Model for the association between trial and patients characteristics
  - Outcome Model

    $\Rightarrow$ **Asymptotically unbiased** when either model is correctly specified
- Achieves the **non-parametric efficiency bound** when both models are correctly specified

  (Shu and Tan, 2018; Dahabreh et al., 2018)

# Simulation Settings (Similar as Dahabreh et al., 2018)

- 10.000 simulations, $n = 500$ (100 in each arm)
- Randomization: $1:1$ in flexible and $1:1:1$ in fixed dosing trial
- 3 covariates: one imbalanced, two balanced between trials
  - $X_1 \sim N(0,1)$ in fixed dosing trial;
    $X_1 \sim N(0.5,1)$ in flexible dosing trial
  - $X_j \sim N(0.5,1)$ in both trials $(j = 2,3)$
- $S|X_1 \sim Ber(expit(0.7X_1))$
- Outcome $Y$ normally distributed with variance 1 and means
  - $2.25X_1 + X_2 + X_3$ when assigned to flexible dose and switched
  - $1.75X_1 + X_2 + X_3$ when assigned to flexible dose and not switched
  - $1.75X_1 + X_2 + X_3$ when assigned to fixed low dose
  - $2.5X_1 + X_2 + X_3$ when assigned to fixed high dose

# Simulation Results

**Impact of Misspecification - Operational Characteristics for treatment effect in switchers**

| Misspecification[2] | Method | Bias | SE |
|---|---|---|---|
| Correct | Proposed Estimator | −0.0002 | 0.0764 |
| | G-computation | −0.0002 | 0.0751 |
| Outcome misspec. | Proposed Estimator | 0.0225 | 0.1002 |
| | G-computation | 0.6430 | 0.1146 |
| SM[3] misspec. | Proposed Estimator | −0.0001 | 0.0757 |
| | G-computation | −0.0002 | 0.0751 |

[2]Misspecification: $X_1$ is replaced by $\log|X_1|$ in the working models

[3]SM: selection model

# Discussion

- **Business case**: enabled evaluation of a potential beneficial effect of higher dose for **subgroup** of patients switching to higher dose
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  - In case of two trials: which baseline factors should be measured?
- **Future work**: improve performance under model misspecification via specialised nuisance parameter estimators

(e.g. Robins, Sued, Lei-Gomez, and Rotnitzky, 2007; Cao, Tsiatis and Davidian, 2009; Vermeulen and Vansteelandt, 2015)

# Thank you for your attention!


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Van Lancker, Vandebosch and Vansteelandt(2020): arXiv:2009.02136

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- Note: similar reasoning for $E(Y^f | T = 1, D = f)$

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- Note: both estimators are equivalent when using a logistic regression for $\pi(\boldsymbol{X}, \gamma)$ [4]

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# Simulation Results

## Operational characteristics for treatment effect in switchers

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| SM[8] misspec. | NP | −0.0001 | 0.0757 |
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[5] Misspecification: $X_1$ is replaced by $\log|X_1|$ in the working models

[6] NP: eff. estimator under non-parametric model

[7] SP: eff. estimator under under semi-parametric model

[8] SM: selection model