Adaptive dose-finding based on safety and feasibility in early phase clinical trials of adoptive cell immunotherapy

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Motivation

Phase I study in newly diagnosed glioblastoma (GBM)

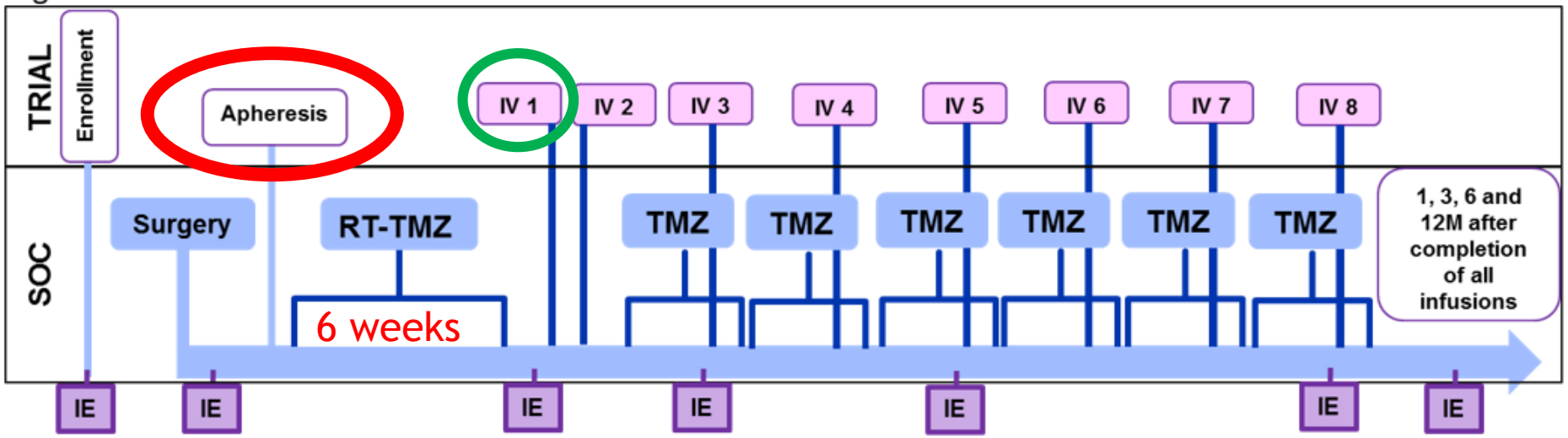
- Activated T cells (ATC) + radiation therapy (RT) + temozolomide (TMZ).
- Four dose levels of ATC infusions: 40, 80, 160, 320 x 10^9 cells.
  - Cells are extracted from patient, expanded, and infused into patient
- Primary objective: identify the feasible and maximum tolerated dose (FMTD), defined by acceptable toxicity and high feasibility.
- Primary endpoints:
  - Dose-limiting toxicity (DLT; yes/no), based on protocol-specific adverse events.
  - Feasibility: enough cells were generated to administer the dose (yes/no).
- How do we identify a safe and feasible dose to carry forward?

Treatment schema

GBM phase I study (NCT03344250)

- T cells are obtained by apheresis and expanded in culture (~2-week process)
- T cells are counted to assess dose feasibility prior to initial infusion

Figure 1. Treatment Schema



Dose feasibility

Example

- Recommended dose for a patient is level 4, **320 x 10^9** cells
- Number of T cells resulting from expansion is **90 x 10^9** cells.
  - Feasible for patient to receive levels 1 and 2
  - Infeasible for patient to receive levels 3 and 4
- Number of cells grown may be < the dose recommended by the design

Study dose level	Cells per infusion	Dose level per patient
1 (start)	5×10^9	40×10^9
2	10×10^9	80×10^9
3	20×10^9	160×10^9
4	40×10^9	320×10^9

90×10^9

Assigned dose

What is done in practice?

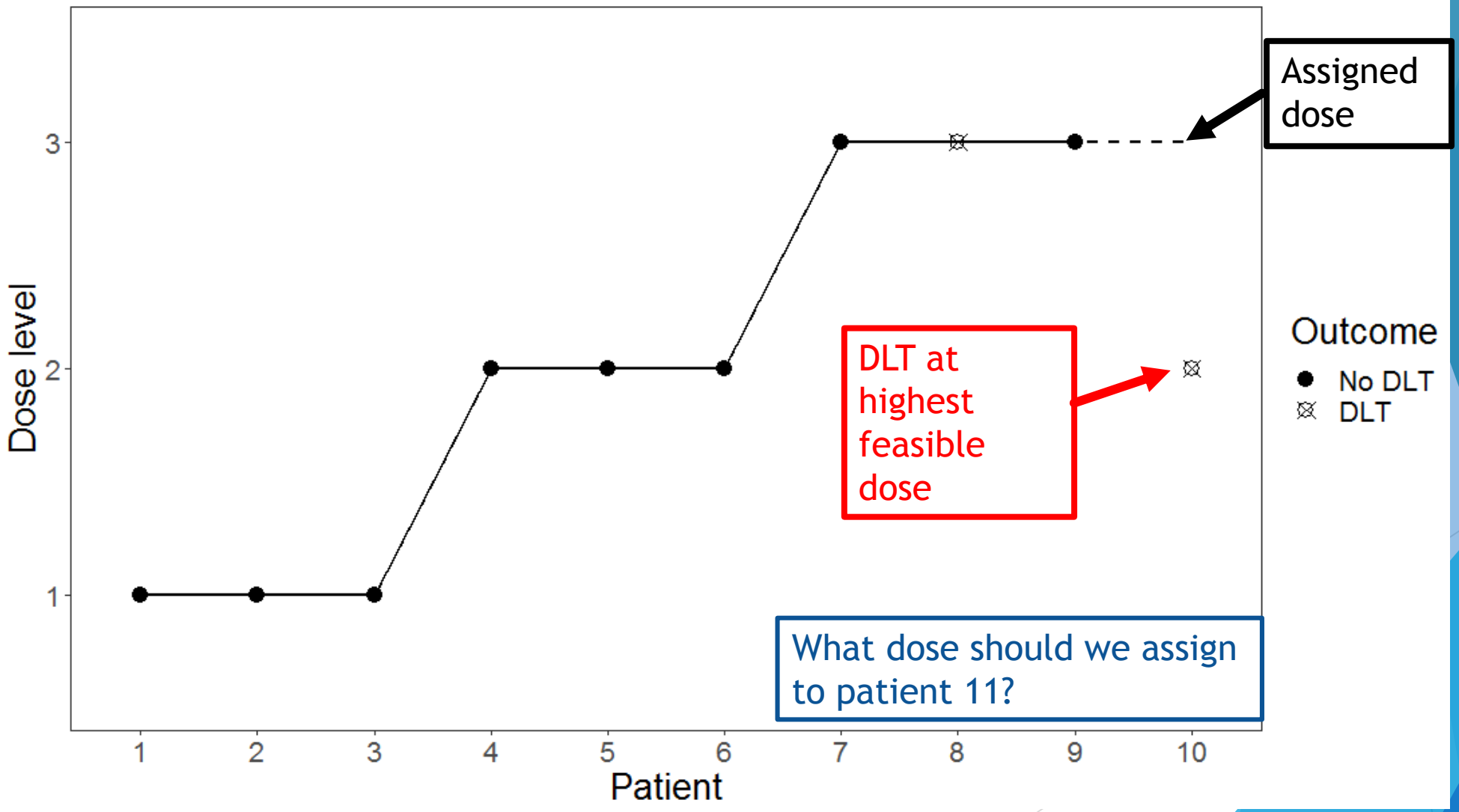
- 3+3 decision rules are often followed.
  - It is not clear how data observed in patients deemed infeasible to receive his/her recommended dose are factored into future dosing decisions.
- Phase I trial of chimeric antigen receptor T cells[1]

"Patients whose chimeric antigen receptor [CAR] T cell product did not meet the dose to which they were assigned did not inform dose escalation but were assessed for toxicity and for all other parts of the study."

- What if a DLT is observed at a lower dose than the assigned dose?

[1]Lee et al, *Lancet*, 2015.

3+3 with infeasible doses



FDA guidance on cell therapy (CT) products

Early-phase clinical trial design considerations

- Early-phase trial objectives
  - "For CT products, these early-phase trials often assess not only safety of specific dose regimens and routes of administration, but also other issues, **such as feasibility of administration…**"
  - "Therefore, sponsors might include design elements that could help foster further product development."
- Feasibility assessments
  - "In these cases [CT products], sponsors should consider designing early-phase trials to identify and characterize **any technical or logistic issues with manufacturing and administering the product**. Such issues may need to be addressed before proceeding with further product development."

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-early-phase-clinical-trials-cellular-and-gene-therapy-products

Existing methods

Safety & feasibility

- Thall et al[2] propose an extension to the continual reassessment method.
  - Model-based design utilizing all observed data in sequential allocation.
  - No evidence that this has method has been used in a real study
  - No accompanying software
- Wages and Fadul[3] method relies on isotonic regression.
  - Simple probability calculations
    - Fast computation.
    - Easy to understand.
  - Good statistical properties.
  - Available R shiny app.

[2]Thall et al, *Biometrics*, 2001.

[3]Wages and Fadul, *Clin Trials*, 2019.

Feasibility

- Let X_k be the number of cells counted for participant k
- $[X_k \geq d_i]$ denotes that enough cells have been grown to treat participant at dose level d_i.
- $[X_k < d_1]$ denotes that there are not enough cells to infuse participant at any dose.
- Let $d_R \in \{d_1, \ldots, d_I\}$ denote the recommended dose level for the next participant based on the updated data
  - If $[X_k < d_R]$, participant is treated at his/her highest feasible dose level

Safety

- For patients with $[X_k \geq d_1]$, DLT data is $\Omega_i = (y_i, n_i)$
  - $y_i = \#$ of observed DLTs at d_i
  - $n_i = \#$ of patients evaluated for DLT at d_i
- From $\mathrm{Beta}(\alpha_i, \beta_i)$ prior, updated DLT probabilities are given by posterior mean

$$\hat{\pi}_i = \frac{y_i + \alpha_i}{n_i + \alpha_i + \beta_i}$$

- Monotonicity is imposed through pool adjacent violators algorithm (PAVA[4])
  - Denote the resulting isotonic estimates as $\tilde{\pi}_i$

[4]Robertson et al, *Order restricted statistical inference*, 1988.

Updating the recommended dose

Based on safety

- The target DLT rate that defines the maximum tolerated dose is π^*
- Algorithm[5] for updating the dose
  - Generally, select the dose with $\tilde{\pi}_i$ closest to π^*
  - Special rules for dealing with ties among the $\tilde{\pi}_i$ and exploring untried doses
- Denote the recommended dose level as d_R

[5]Conaway et al, *Biometrics*, 2004.

Modeling feasibility probabilities

- At dose level d_i, feasibility data is $\mathbb{D}_i = (z_i, m_i)$
  - $z_i = \#$ of patients feasible to receive d_i
  - $m_i = \#$ of patients accrued and have had cells obtained
- Probability of feasibility at dose level i is θ_i
- From $\text{Beta}(\tau_i, \nu_i)$ prior, posterior distribution of θ_i is

$$\theta_i | \mathbb{D}_i \sim \text{Beta}(\tau_i + z_i, \nu_i + m_i - z_i)$$

- Based on minimum acceptable feasibility rate θ^*, we can compute

$$\Pr(\theta_i < \theta^* | \mathbb{D}_i) = \mathcal{B}(\theta^*; \tau_i + z_i, \nu_i + m_i - z_i)$$

Trial conduct

- Treat participant k at highest feasible dose if $X_k < d_R$ or d_R if $X_k \geq d_R$
- Stop the trial for safety if

$$\Pr(\pi_1 > \pi^* | \Omega_1) = 1 - \mathcal{B}(\pi^*; \alpha_1 + y_1, \beta_1 + n_1 - y_1) > p_T$$

- Stop the trial for infeasibility if

$$\Pr(\theta_1 < \theta^* | \mathbb{D}_1) = \mathcal{B}(\theta^*; \tau_1 + z_1, \nu_1 + m_1 - z_1) > p_F$$

- Otherwise accrual continues until…
  1. N participants have been infused and evaluated for DLT or
  2. M participants have had cells extracted

Study conclusion

Selecting the FMTD

- Denote the recommended dose from the final DLT data as d_R.
- From the final feasibility data, the set of feasible doses is given by

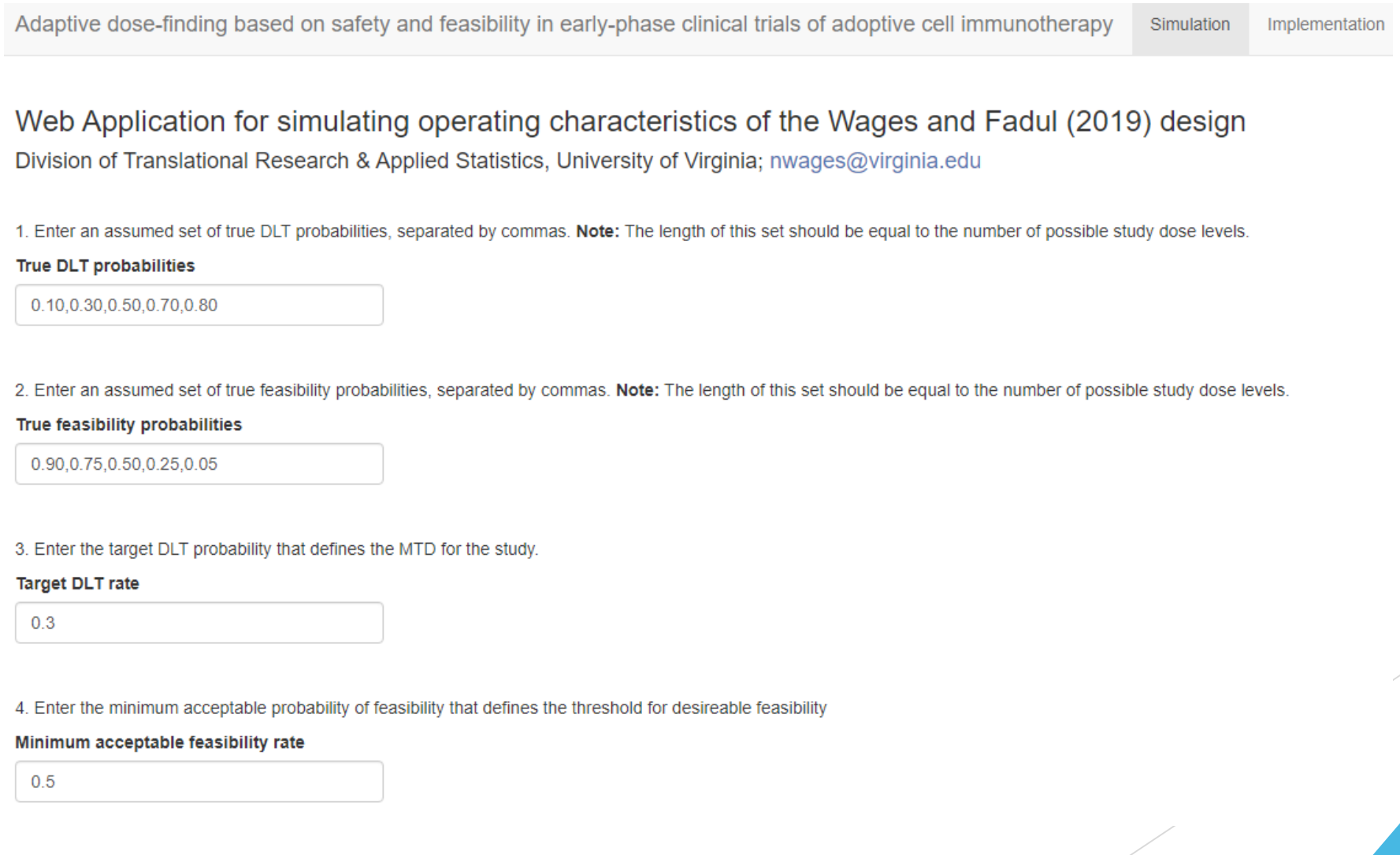
$$\mathcal{F} = \{d_i : \Pr(\theta_i < \theta^* | \mathbb{D}_i) \leq p_F\}$$

- Denote the highest dose in $\mathcal{F}$ as d_F.
- The estimated FMTD at the end of the study

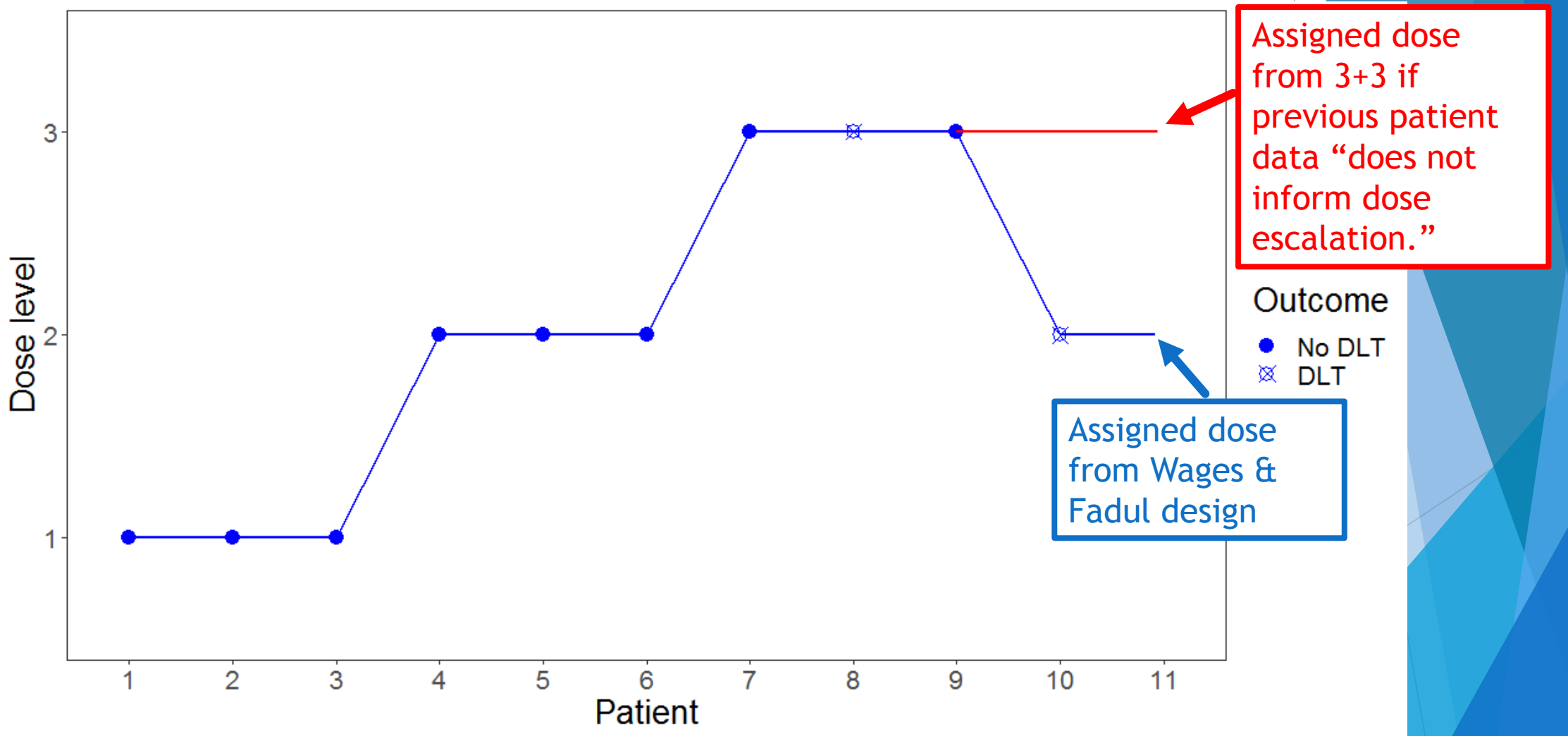
$$\widehat{FMTD} = \min(d_R, d_F)$$

R Shiny app

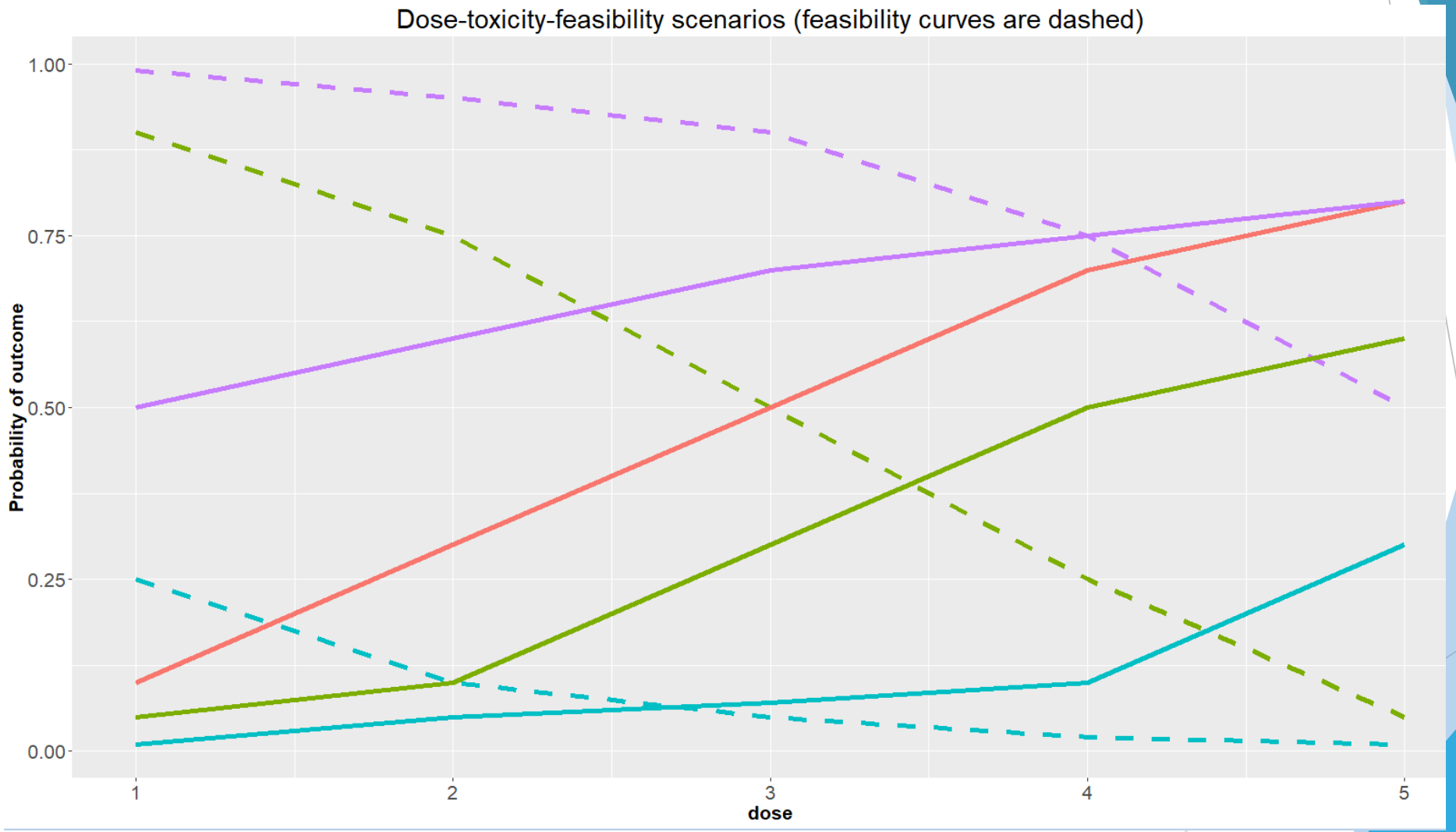
http://uvatrapps.uvadcos.io/wfdesign/



Revisiting example

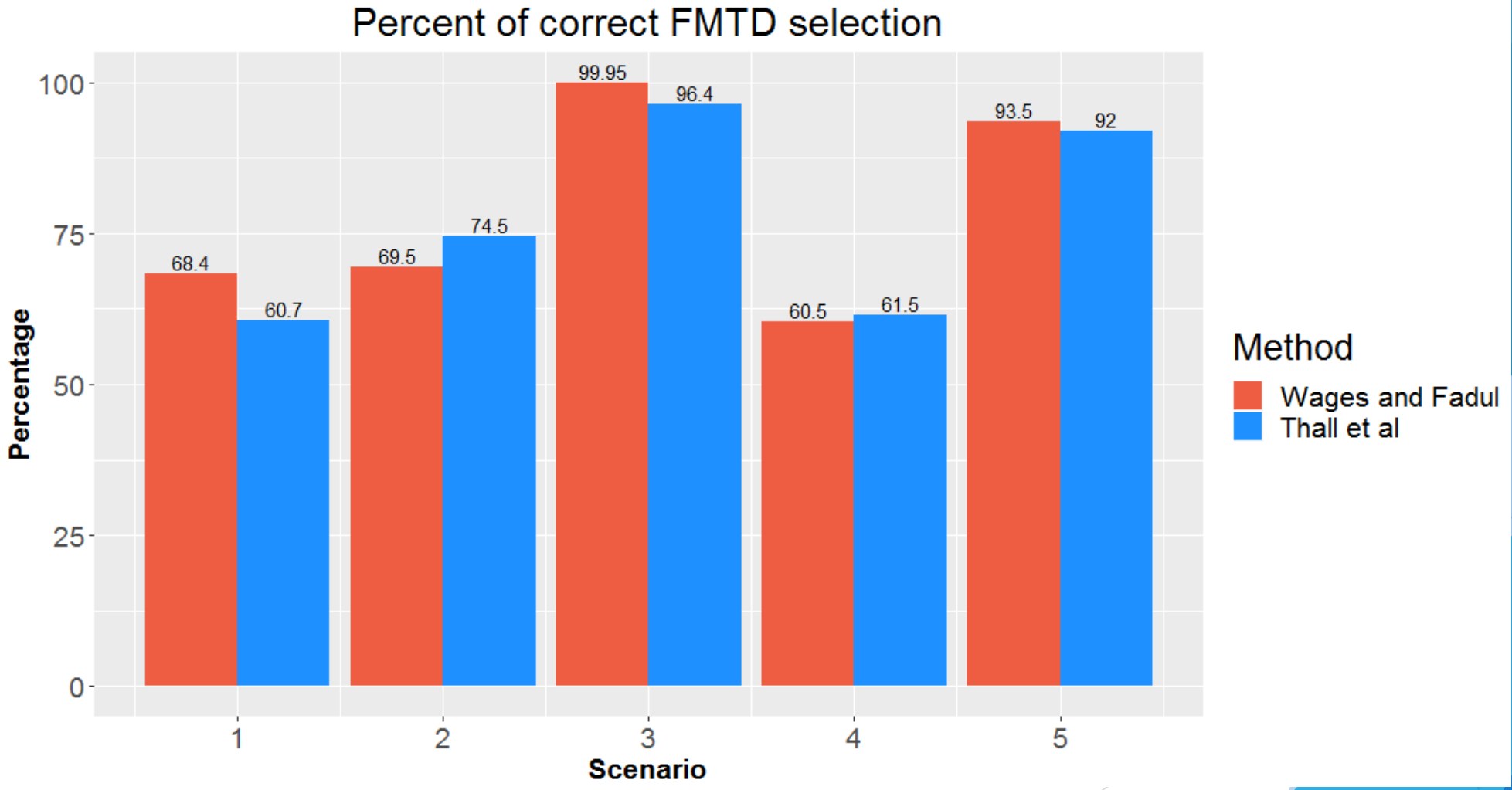


Simulation scenarios[3]



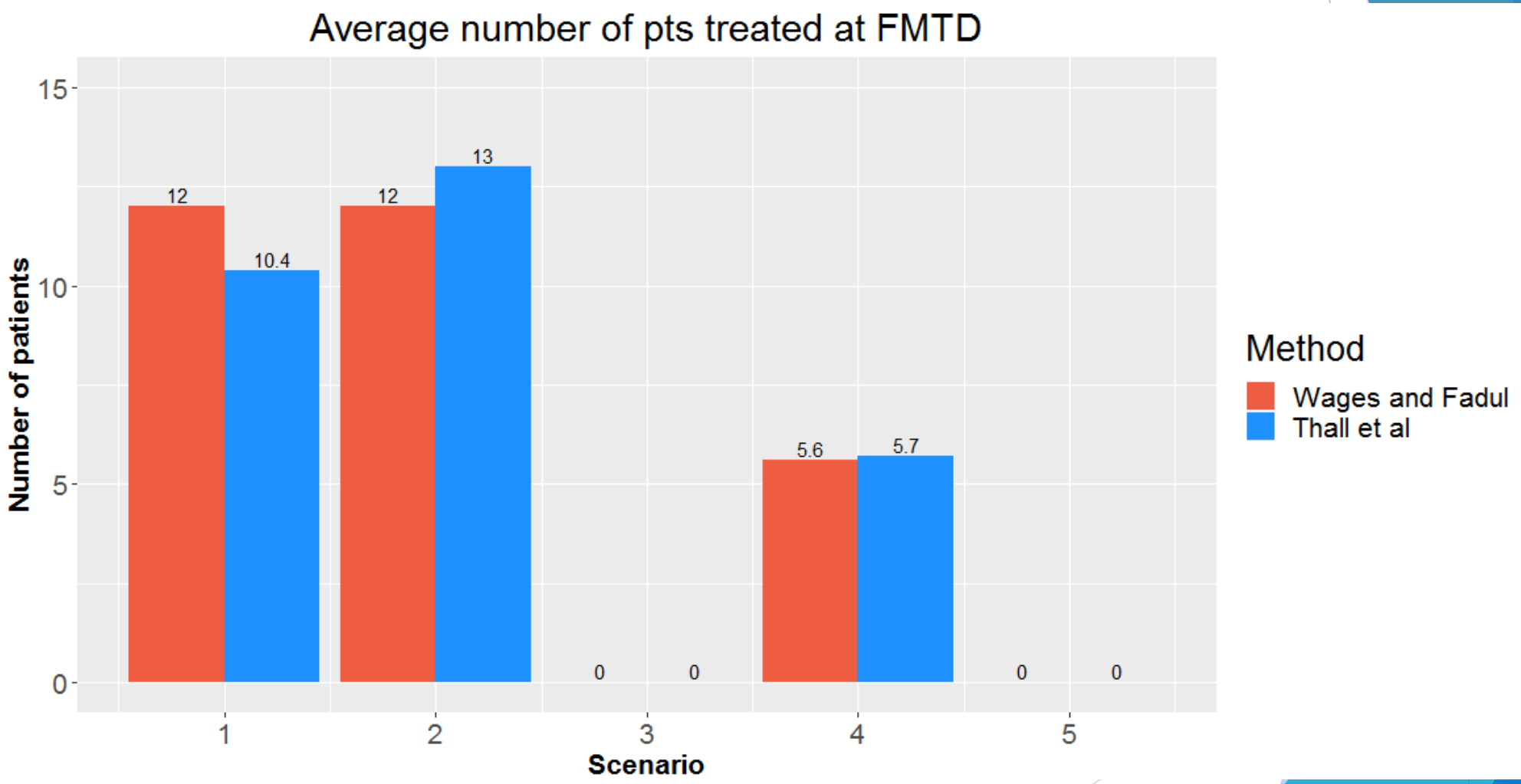
[3]Wages, Fadul, *Clin Trials*, 2019.

Results[3]



[3]Wages, Fadul, *Clin Trials*, 2019.

Results[3]



[3]Wages, Fadul, *Clin Trials*, 2019.

Concluding remarks

- A new adaptive Phase I design that accounts for both safety and feasibility
  - Mathematically simple and feasible to implement
  - Fast computation (~20s to generate 10,000 simulated trials)
  - User-friendly available software
  - Easy to explain to clinical colleagues
- https://faculty.virginia.edu/model-based_dose-finding/
  - R code and shiny web application
  - Slides are available for download

Recently Published[3]

Article

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Adaptive dose-finding based on safety and feasibility in early-phase clinical trials of adoptive cell immunotherapy

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Abstract

Background/aims: Dose feasibility is a challenge that may arise in the development of adoptive T cell therapies for cancer. In early-phase clinical trials, dose is quantified either by a fixed or per unit body weight number of cells infused. It may not be feasible, however, to administer a patient's assigned dose due to an insufficient number of cells harvested or functional heterogeneity of the product. The study objective becomes to identify the maximum tolerated dose with high feasibility of being administered. This article describes a new dose-finding method that adaptively accounts for safety and feasibility endpoints in guiding dose allocation.

[3]Wages, Fadul, *Clin Trials*, 2019.

References

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