Challenges of underdosing control in dose-escalation studies for DNA-based gene therapies

Biopharmaceutical Applied Statistics Symposium (BASS)

Quang Nguyen, Rong Liu

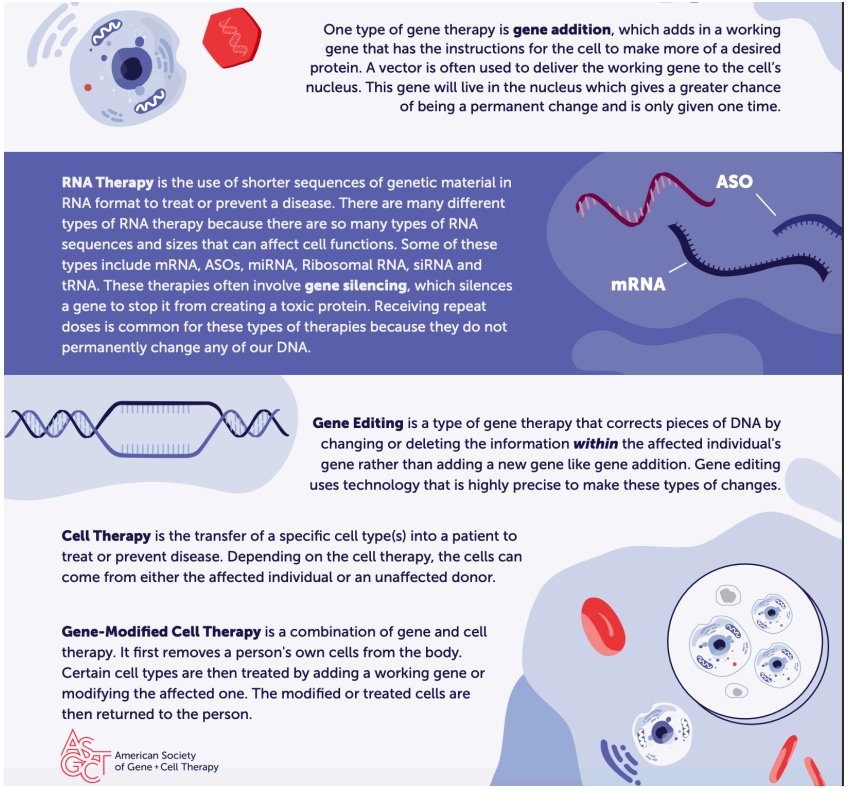
Biostatistics and Data Management, Regeneron Pharmaceuticals

NOV 2024

REGENERON®

Gene therapy is characterized by inducing significant changes in host genetics

Challenges and opportunities for developing novel gene therapies for rare disease



Human gene therapy seeks to **modify or manipulate** the expression of a gene or to alter the biological properties of living cells for therapeutic use.

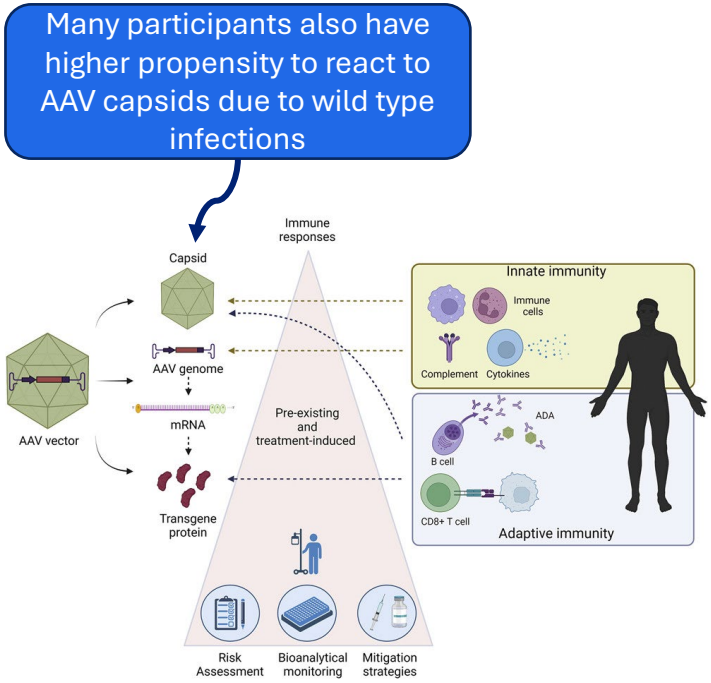
DNA-based therapies, such as **gene editing** or **gene addition**, are challenging since they **permanently change** cellular genetics where therapies can be given **only one time.**

Source: American Society of Gene and Cell Therapy

Immunogenicity can prevent patients from receiving future gene therapies from the same platform

After treatment, many patients will **develop antibodies** targeting various components of the gene therapy delivery system.

Immunogenicity can **reduce efficacy** of the intended activity of the transgene product, while also **increasing the potential for serious and severe adverse events**.

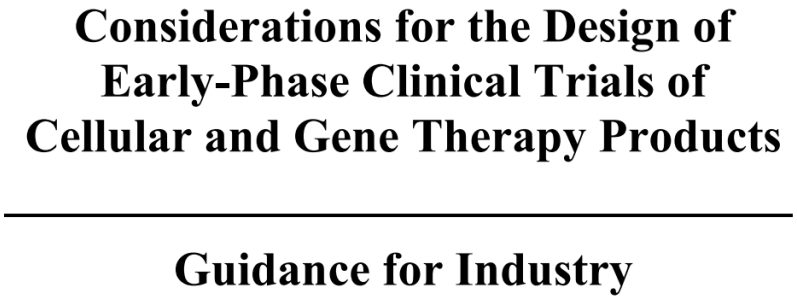


Yang et al. Molecular Therapy. 2022

REGENERON®

Regulatory perspective for design of gene therapy clinical trials from published guidelines

- The dose exploration strategy during clinical phase can be difficult to ascertain prior to conducting clinical trials.
  - Identifying the MTD during early phase trials should not be ruled out since there is considerable risk of treating patients with subtherapeutic dose.
  - Regulatory agencies agree that due to the extended activity of CGT products, re-dosing is not an acceptable risk.
- Early phase I dose escalation studies can opt to not having a control arm due to ethical considerations. However, this does not mean that future registrational trials are always single arm trials.



There is a lot of uncertainty!

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products. FDA

Addressing underdosing risk can be challenging from a data perspective

- Treatment is targeted as well as systemic, where the desired product is produced in the liver and then circulated throughout the body.
- Gene therapies are developed to target rare and orphan diseases.

Clinically relevant efficacy outcomes might not be available during the escalation phase

Limited number of participants to be recruited into large cohorts.

Addressing underdosing risk can be challenging from a data perspective

Clinically relevant efficacy outcomes might not be available during the escalation phase.

Limited number of participants to be recruited into large cohorts.

Continuous PD markers (concentration/activity of the protein in circulation) can be used to guide dose escalation.

Utilizing acceleration strategies or relying more on model-based designs.

<u>Objectives</u>: How can we design clinical trials using **continuous markers to** identify the correct dose to move forward while limiting participant **exposure to suboptimal dose ranges**?

Objectives: How can we design clinical trials using **continuous markers to** identify the correct dose to move forward while limiting participant **exposure to suboptimal dose ranges**?

Using simulated scenarios we will evaluate:

- The operating characteristics of existing approaches for this scenario
- Evaluate whether additional rule-based or model-assisted components can be used to simplify designs.
- Evaluate whether acceleration strategies can be used to avoid underdosing while still recommending the correct dose to further develop.

Hypothetical clinical trial scenario for simulation

We assume a hypothetical clinical trial where we are evaluating a DNA-based gene therapy for a rare disease.

N per cohort = 3
1-dose level skipping allowed

Dose 4:
60 (x10^{10}vg/kg)

Dose 3:
45 (x10^{10}vg/kg)

Dose 2:
30 (x10^{10}vg/kg)

Dose 1:
15 (x10^{10}vg/kg)

The concentration of the transgene protein circulating in plasma can be available during dose escalation, which gives us a continuous PD marker, denoted as W_i

We will evaluate toxicity by the presence/absence of dose-limit toxicities, denoted as $Y_i = \{0,1\}$

Stopping criteria:

- If no dose can be obtained due to toxicity of futility (design-specific)
  - If the decision is to escalate to a toxic dose or to de-escalate to a futile dose, we will choose to stay at the current dose for an additional cohort.
- Total sample size reaches 30
- 3 cohorts have been dosed at a given dose level

Hypothetical clinical trial scenario for simulation (cont.)

We assume a hypothetical clinical trial where we are evaluating a DNA-based gene therapy for a rare disease.

The concentration of the transgene protein circulating in plasma can be available during dose escalation, which gives us a continuous PD marker, denoted as W_i

$$W \sim LogNormal(\mu_{log}, \sigma^2_{log})$$

$\mu_{log}, \sigma^2_{log}$ computed from pre-specified mean as well as coefficient of variation of 0.5. Prior knowledge indicates that the maximum possible value for the biomarker is 200

We will evaluate toxicity by the presence/absence of dose-limit toxicities, denoted as $Y_i = \{0,1\}$

$$Y \sim Bernoulli\ (p(x))$$

$p(x)$ is the pre-specified DLT probability per dose level.

Summary of evaluated designs

A non-exhaustive list chosen primarily on ease of available software for implementation

Implementation of the modeling component of these designs can be easily accessible through the crmPack package, developed by industry professionals

Considered designs	Efficacy Outcome	Toxicity Outcome	Escalation/De-escalation Rules
Bekele and Shen 2005 (BS)	Model-based, using the joint modeling using the latent variable parameterization of probit regression by Albert and Chib		Next dose is assigned based on assessment of safety and futility with the highest posterior probability in the target range
Yeung and Jaki 2015 (YJ)	Model-based, using a log-log model for efficacy outcomes.	Model-based, using the two-parameter logistic regression model	Based on assessment of safety as well as a gain function.
Checkerboard – (CB)	Model-based, using the joint modeling using the latent variable parameterization of probit regression by Albert and Chib		Keyboard approach with a pre-specified decision table based on posterior densities
Customized design combining BOIN with modeling continuous outcomes	Model-based, allowing for borrowing between doses.	BOIN based	Next dose is assigned based on a modification of BOIN decision rules.

Approaches to perform dose escalation using binary toxicity and continuous efficacy responses

CRM Designs modeling the dose-response relationship

Bekele and Shen 2005

Jointly models toxicity and efficacy using a probit model with the Albert and Chib parameterization.

$$Probit[p(x)] = \beta_{Z_1} + \beta_{Z_2} \log\left(\frac{x}{x^*}\right) + \epsilon$$
$$w(x) \sim N(f(x), \sigma_w^2)$$
$$f(x) = \beta_{W_i}$$
$$\beta_{W_i} - \beta_{W_{i-1}} \sim N\left(0, (x_i - x_{i-1})\sigma_{\beta_w}^2\right)$$

Acceptable doses are selected based on the following criteria: For a given dose k, target toxicity probability π_t, minimum sample size m, and minimum efficacy level W_{min}

$$P\left(\beta_{W,k} > W_{min}^*\right) > \delta_1$$
$$P(p(x) < \pi_t | Data, n_k \geq m) > \delta_2$$

Or

$$\Pr(p(x)_{k-1} < \pi_t | \, data, n_k < m, n_{k-1} \geq m) > \delta_3$$

The acceptable dose with the highest probability of efficacy in the target range is chosen.

Yeung and Jaki et al. 2015

Separately models the toxicity and efficacy

$$\Pr(Y = 1) = \frac{\exp(\phi_1 + \phi_2 \log(x))}{1 + \exp(\phi_1 + \phi_2 \log(x))}$$

$$W_i = \theta_1 + \theta_2 \log(\log(x))$$

Decision rules based on the dose that generates the maximum gain that is not toxic.

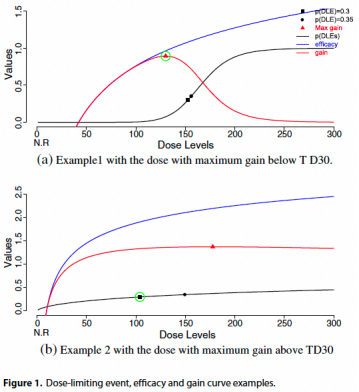


Figure 1. Dose-limiting event, efficacy and gain curve examples.

Yeung and Jaki. 2015

- Estimates the dose that has the highest mean posterior probability closest to the target DLT rate.
- Computes the dose that maximizes the gain function.

$$G(j) = \frac{\theta_1 + \theta_2 \log(\log(x))}{1 + \exp(\phi_1 + \phi_2 \log(x))}$$

- Selects the smaller of the two doses

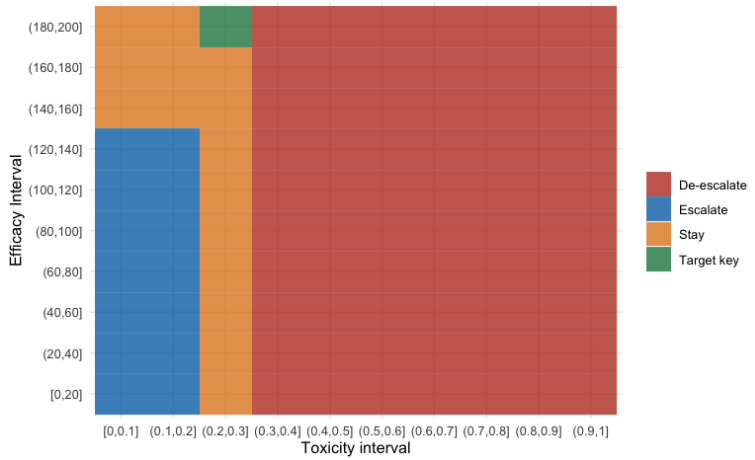
Approaches to perform dose escalation using binary toxicity and continuous efficacy responses (cont.)

Designs utilizing simpler decision rules for escalation and de-escalation purposes

Checkerboard (Yi and Yuan 2020)

Utilizes the joint modeling approach as specified in Bekele and Shen.

"Keys" (similar to Keyboard/mTPI-2 design) are defined apriori, including the **target key**. Decisions are made based on which key is the "strongest" key, or the key with the highest posterior density for each toxicity/efficacy dimension.



Custom BOIN

Modeling is only performed for the efficacy endpoint.

$$W|\beta_w, \sigma_w^2 \sim N(X * \beta_w, \sigma_w^2 * I)$$

where X_{ij} indicates the assignment of patient i to dose j.

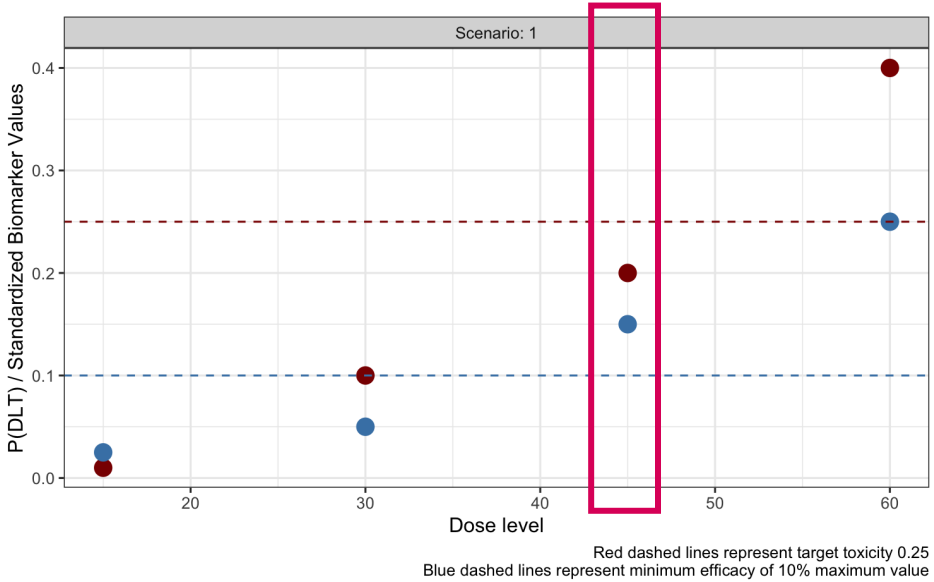
$$\beta_{w_j} - \beta_{w_{j-1}} \sim N(0, \sigma_{\beta_w}^2)$$

This model is similar to the BS and Checkerboard approaches, however without estimating the correlation between efficacy and toxicity.

We then combine this with BOIN decision rules for safety, based on target probability of 0.3 (since our cohort size is 3).

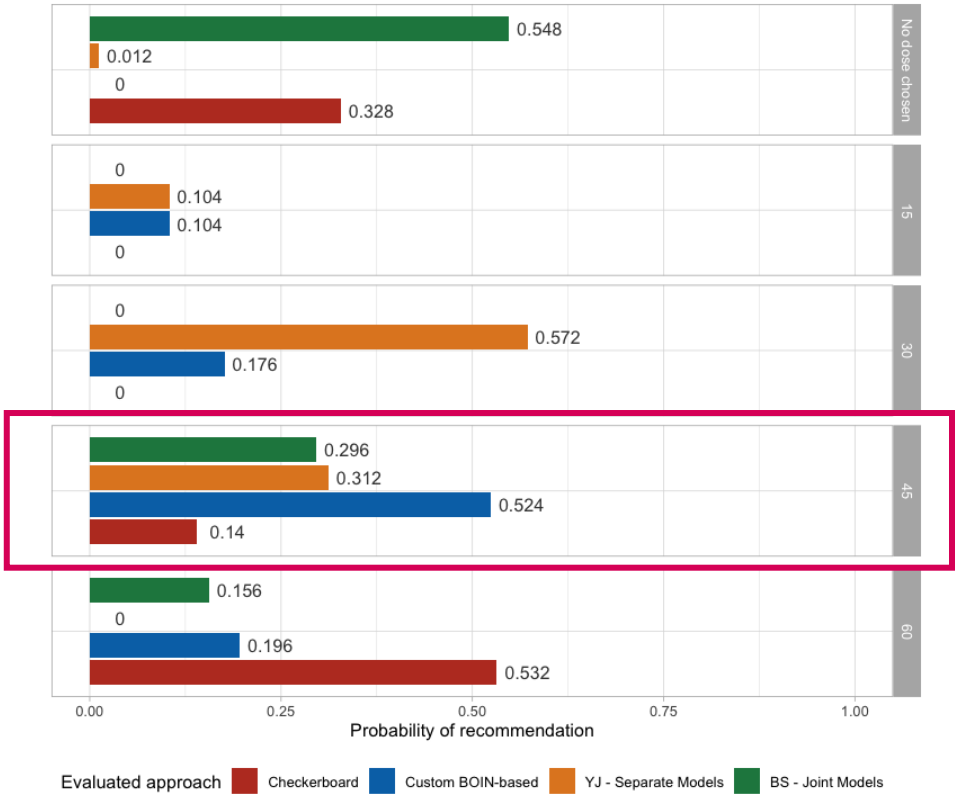
Decision Table	DLT rate $\leq \lambda_e$	$\lambda_e \leq$ DLT rate $\leq \lambda_d$	DLT rate $\geq \lambda_d$
$\mathbf{Pr}(\boldsymbol{W} \geq \boldsymbol{W_{min}} \mid \boldsymbol{Data}) \geq \mathbf{0.5}$	Escalate	Stay	De-escalate
$\mathbf{Pr}(\boldsymbol{W} \geq \boldsymbol{W_{min}} \mid \boldsymbol{Data}) \leq \mathbf{0.5}$	Escalate	Escalate	De-escalate

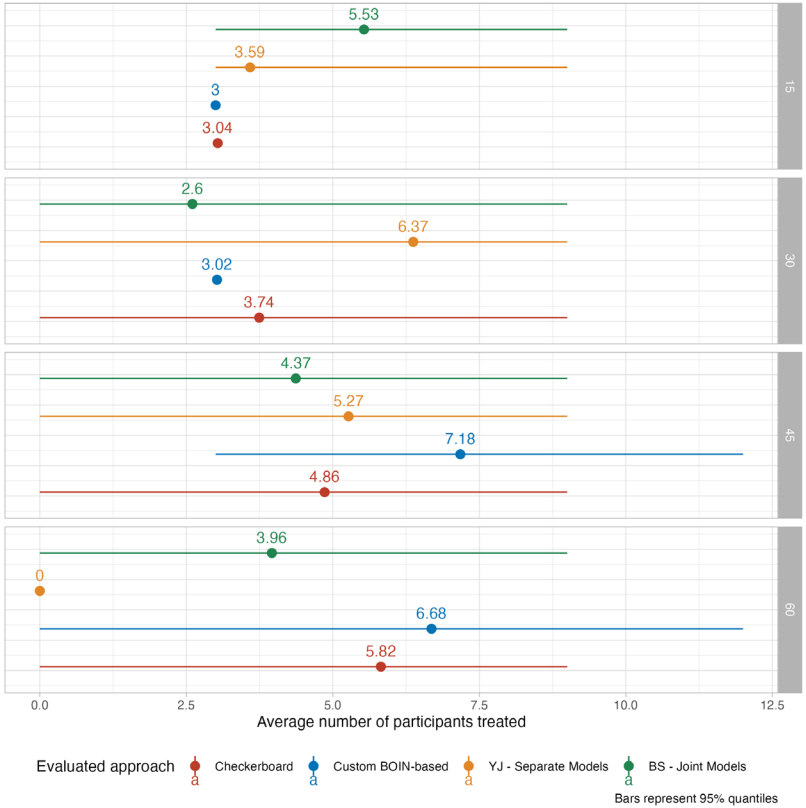
A ”typical” scenario with monotonically increasing efficacy and toxicity



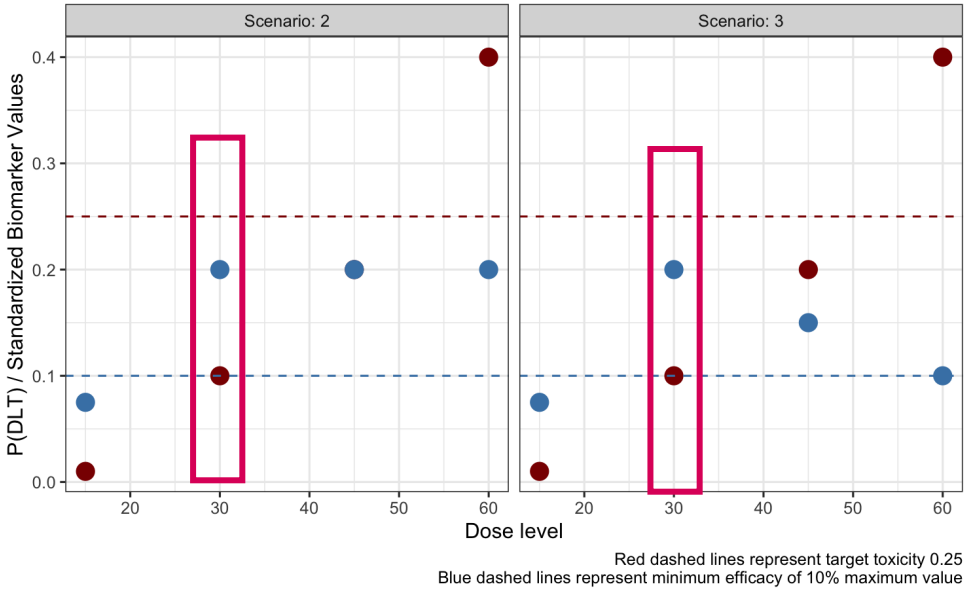
In this scenario, doses 1 and 2 are sub-optimal and below the pre-defined minimum threshold. Dose 4 is the toxic dose ($\Pr(DLT) = 0.4$). **Dose 3 is the optimal biological dose (OBD)**

BOIN is more likely to identify the correct OBD, while also limiting participant exposure to subtherapeutic dose.





Scenarios with non-monotonic efficacy

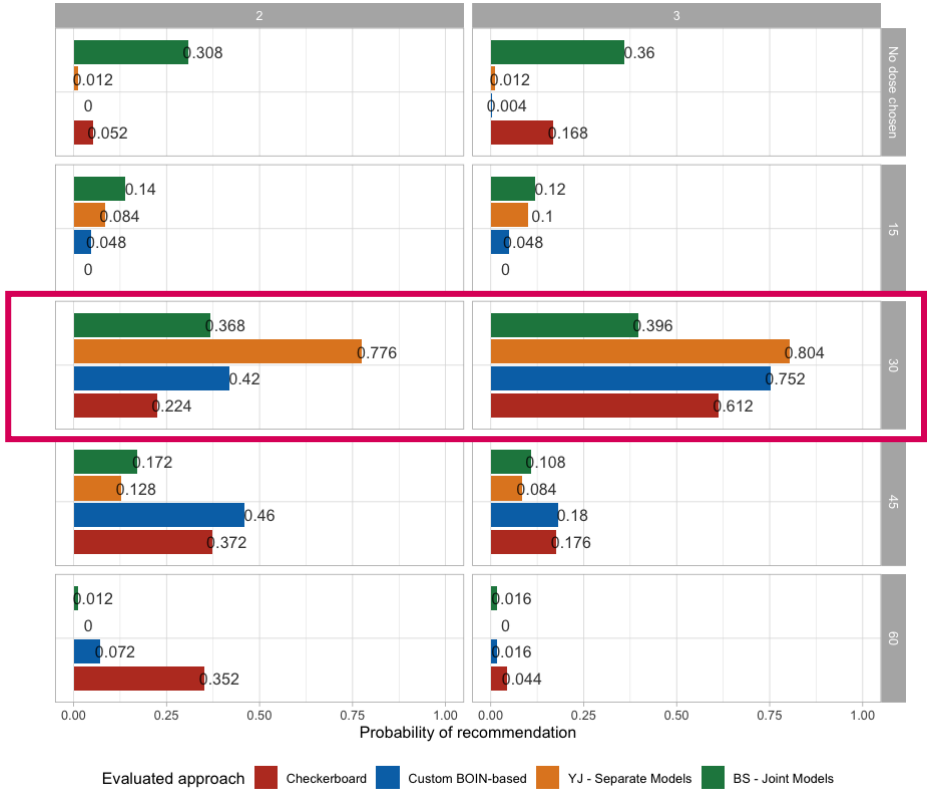


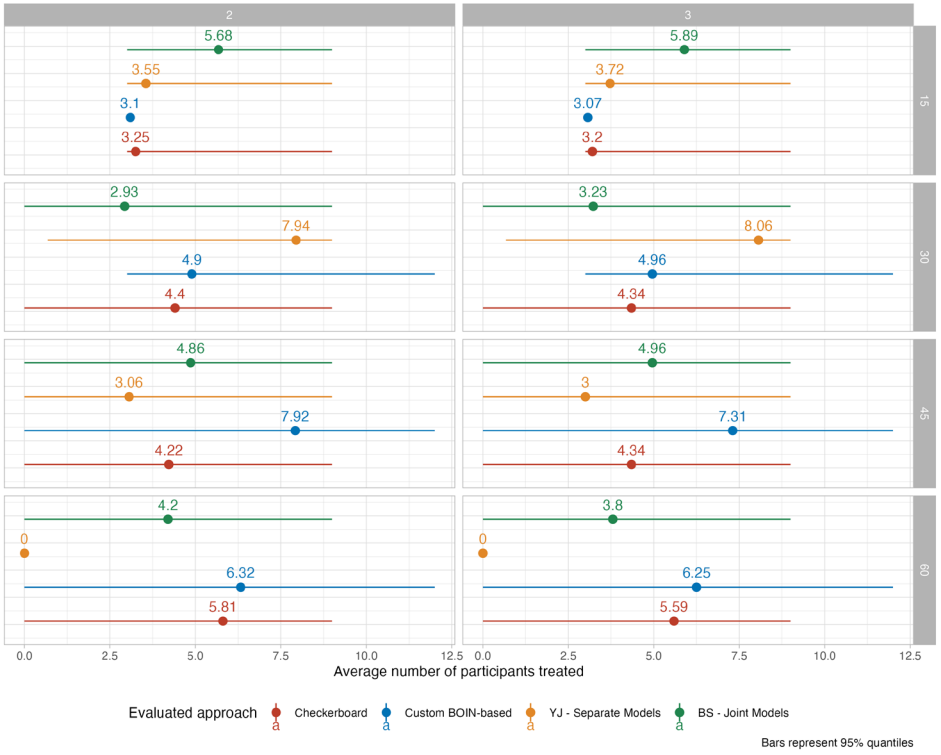
Scenario 2: Efficacy plateaus at dose 2 after 20% of maximum efficacy has been reached

Scenario 3: Efficacy decreases after dose 2 after 20% of maximum efficacy has been reached.

Both scenarios have toxicity monotonically increasing with dose 4 being the toxic dose ($\Pr(DLT) = 0.4$). **Dose 2 is the OBD**.

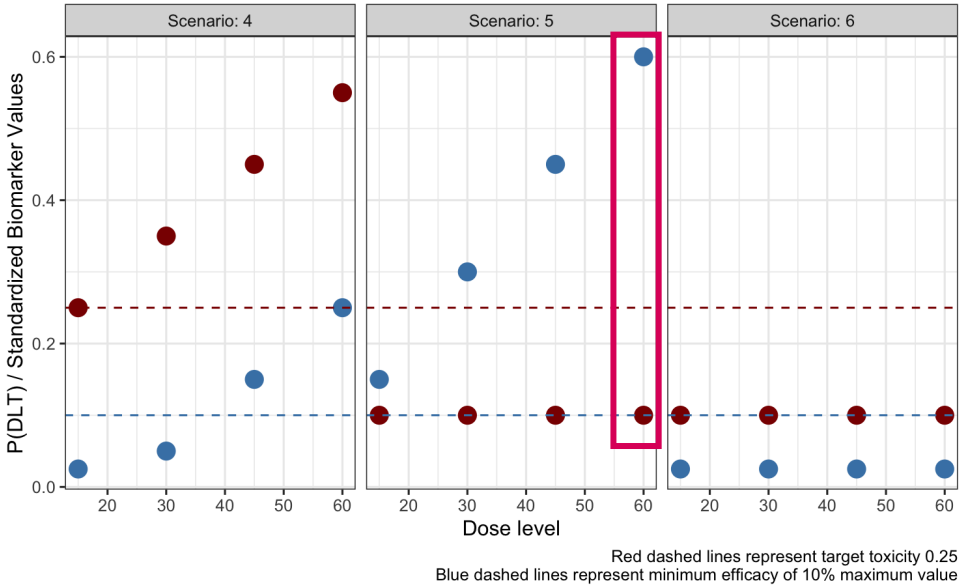
YJ design outperforms others when there exists plateau or decreasing efficacy with increasing dose.





REGENERON

Scenarios with all toxic or subtherapeutic doses

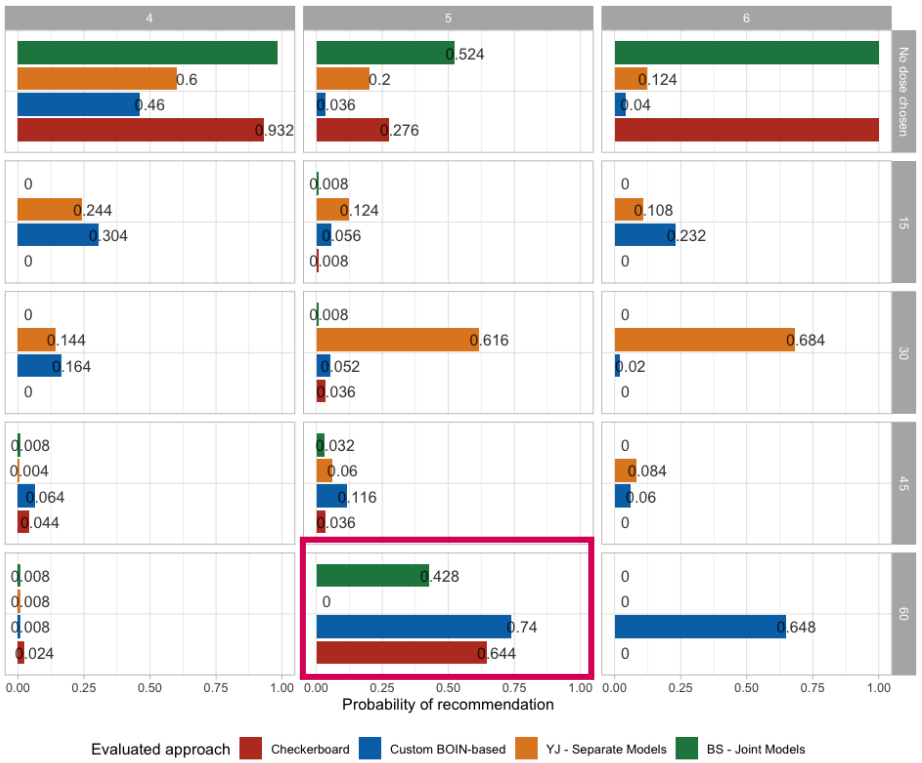


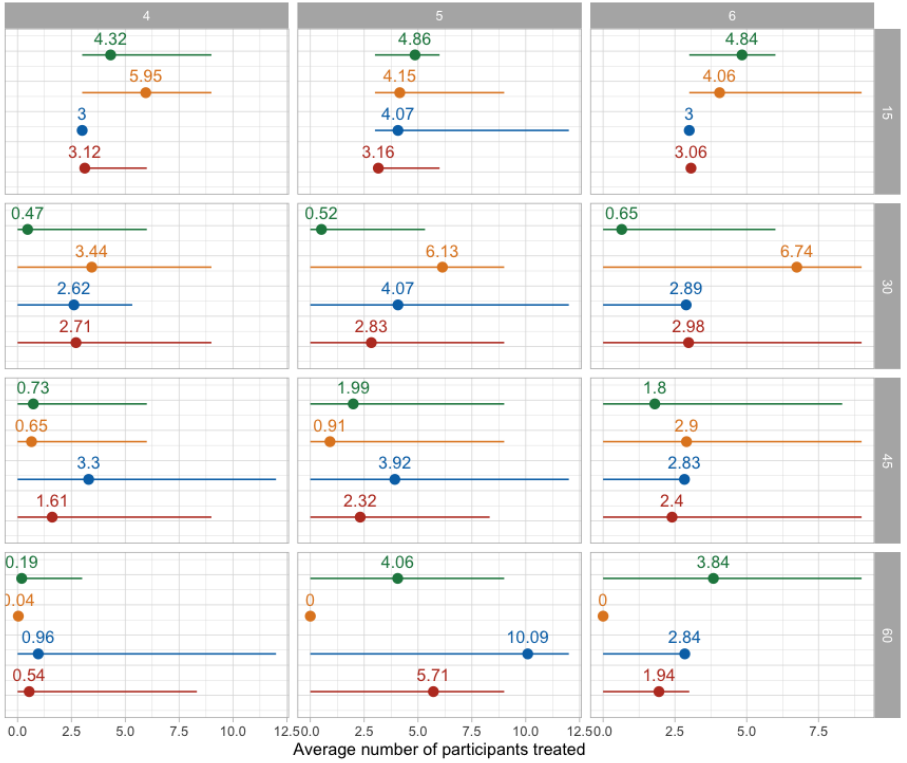
Scenario 4: There is a monotonically increasing efficacy, but all doses are toxic. **No dose is the OBD**.

Scenario 5: All doses are efficacious, and no doses are toxic. **Dose 4 (top dose) is the OBD**.

Scenario 6: All doses are subtherapeutic but are also not toxic ($\Pr(DLT) = 0.1$). **No dose is the OBD**.

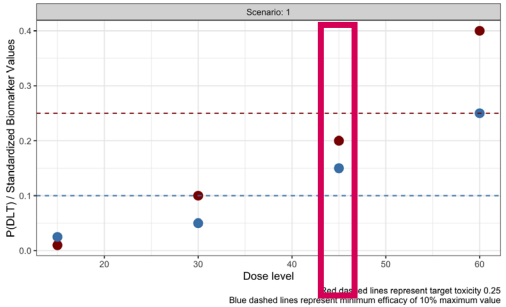
Joint models are generally more conservative and does not recommend any doses to move forward in special scenarios

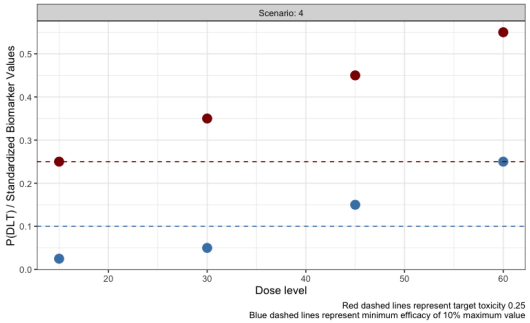




Evaluating ”accelerated titration” as a step for moving beyond subtherapeutic dose

Evaluated against scenarios 1 and 4





One participant is enrolled at the lowest dose. If that participant:

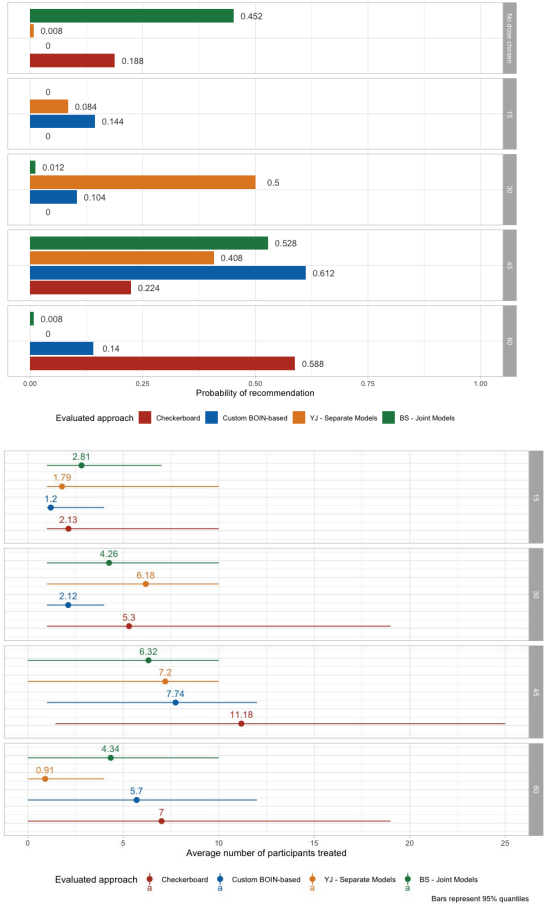
- Did not experience any DLT event or multiple toxicity events of grade II.
- Did not achieve the minimum efficacy threshold

Then the next participant will be dosed at a higher dose. The acceleration step will stop and cohorts of size 3 will be enrolled as specified when either:

- Participants experienced a DLT event or 2 toxicity events of grade II
- If the minimum efficacy threshold has been reached.

Standard

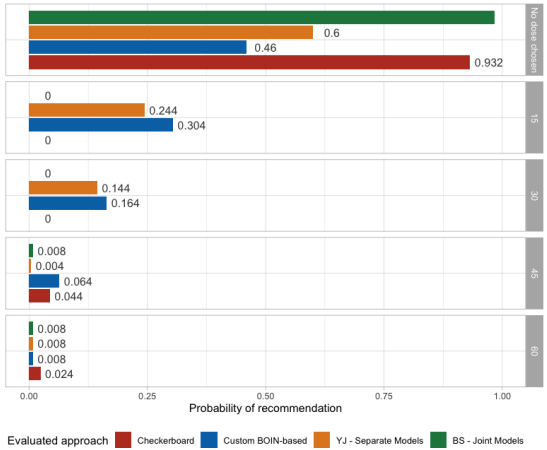
With accelerated titration

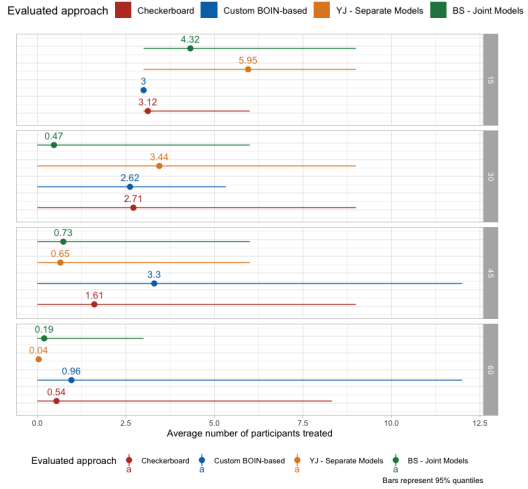


Utilizing acceleration can assist in reducing sample size for subtherapeutic doses and increase the probability of recommending the correct dose

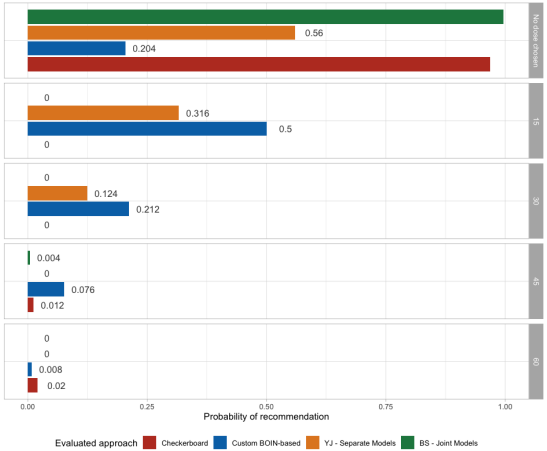
REGENERON®

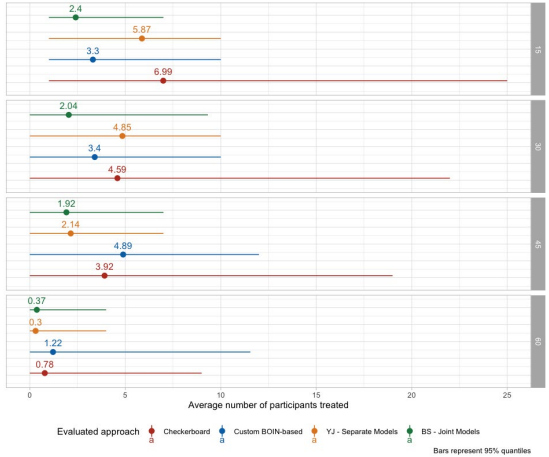
Standard





With accelerated titration





Acceleration strategy can inadvertently increased exposure to toxic doses

REGENERON®

Summary of results

- Continuous efficacy outcomes means that the designs are never completely “model assisted”, meaning that the decision table cannot be pre-specified during the protocol/SAP drafting phase.
- Joint modeling approaches can be conservative, requiring generally more participants while also less likely to recommend a dose due to low sample sizes.
- Utilizing BOIN as the backbone for escalation can allow for rapid escalation but can run into issues if the majority of doses are toxic.
- Acceleration can be appropriate strategy to mitigate underdosing in dose escalation trials in gene therapies.

Challenges in implementing design strategies with continuous PD markers

- Choosing a threshold for the target PD/efficacy response can be challenging.
  - For the minimum activity level, the choice can be driven by the variability and level of what is considered normal activity of the PD marker.
  - There is not always clear evidence for which can be the **target** for PD levels, since there might not be a clear correlation between PD marker and efficacy outcomes.

- Due to low sample size, prior choice can have an outsized impact on the outcome of dose escalation process, especially for more challenging models.
  - The decision to elicit pessimistic or optimistic priors can alter the operating characteristics of the trial.
  - Evaluate and specify multiple types of priors and evaluate prior predictive distributions.

Thank you!

Quang Nguyen
Regeneron Pharmaceuticals, Inc.
quang.nguyen1@regeneron.com

Supplemental Information

Implementation Details

Prior specifications

For Bekele and Shen 2005, as well as for Checkerboard:

$$\beta_{Z_1}, \beta_{Z_2} \sim MVN\left(\begin{bmatrix}-1\\0\end{bmatrix}, Diag(2)\right)$$

$$\sigma_{\mathrm{w}}^2 \sim IG(0.1, 0.1)$$
$$\rho \sim Uniform(0,1)$$
$$\beta_{W_0} = 0.3989$$

For Yeung et al. 2015, the prior for both efficacy and toxicity endpoints are based on the pseudo data approach (Whitehead et al.). For toxicity, we specified that the lowest dose and highest dose have DLT probabilities of 0.16 and 0.25 (respectively). For efficacy, we specified that the lowest dose and the highest dose have mean efficacy of 10% maximum efficacy, and 100% maximum efficacy, respectively.

For the custom BOIN approach, we used default priors as specified in the crmPack function for the EffFlexi model (https://openpharma.github.io/crmPack/main/reference/EffFlexi-class.html)

Whitehead et al. Biostatistics. 2001