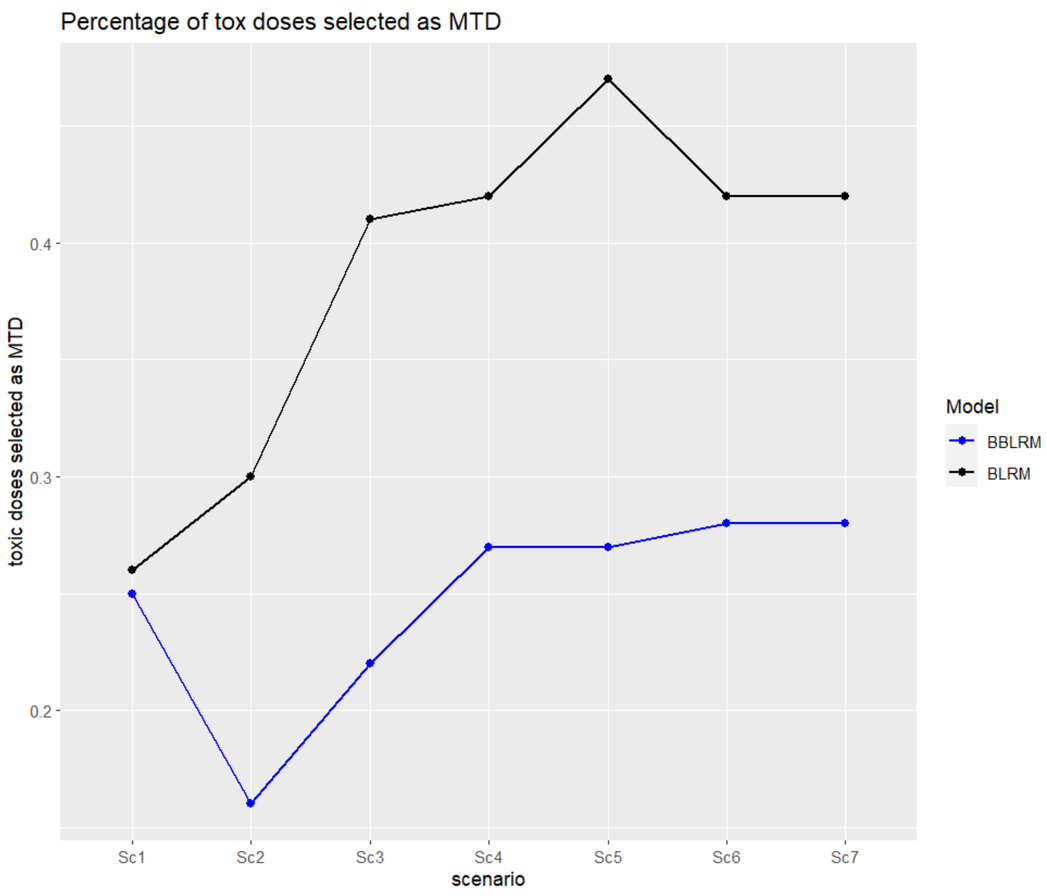
Involving **clinicians** in model-based designs with **Non-DLT Adverse Events Integration**: **A safer approach** to increase the performance of dose-escalation Phase I cancer trials.

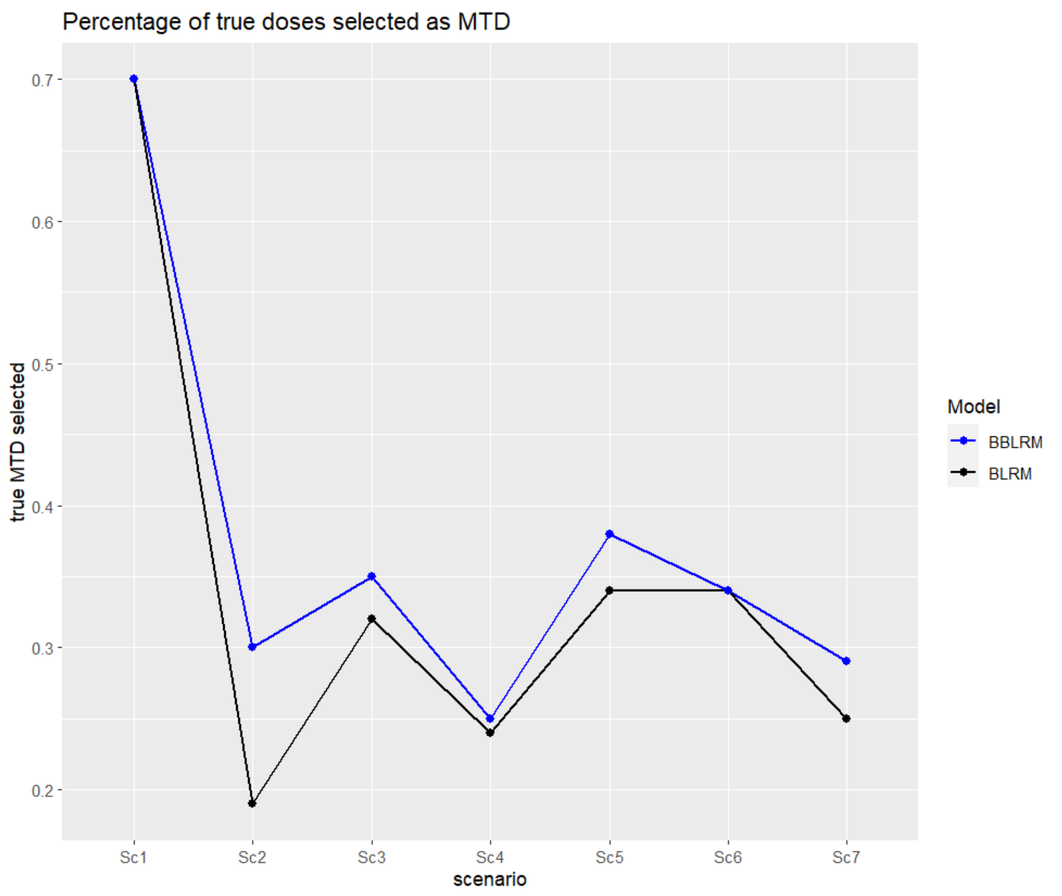
Enhancing Dose Selection in Phase I Cancer Trials: Extending the Bayesian Logistic Regression Model with Non-DLT Adverse Events Integration

Background: In phase 1 oncology trials the main goal is the **identification of the maximum tolerated dose (MTD)**, with particular **attention to the patient's safety**. In this context, clinicians are often reluctant to adopt model-based design, preferring the more conservative but, often, less efficacious rule-based approach, like 3+3.

Result 1: Up to **-21% of toxic doses** selected as MTD*.



Result 2: Up to **+11%** in selecting **the correct** MTD*.



*Note: Results obtained from a simulation of seven scenarios varying the toxicity probabilities assumed for each dose and the true MTD. We considered the same vector of nine doses across the scenarios.

Methods

Starting point: Standard Bayesian Logistic Regression Model (BLRM) with stopping ruled introduced by Zhang et al. 2022 accounting for underdose probability:

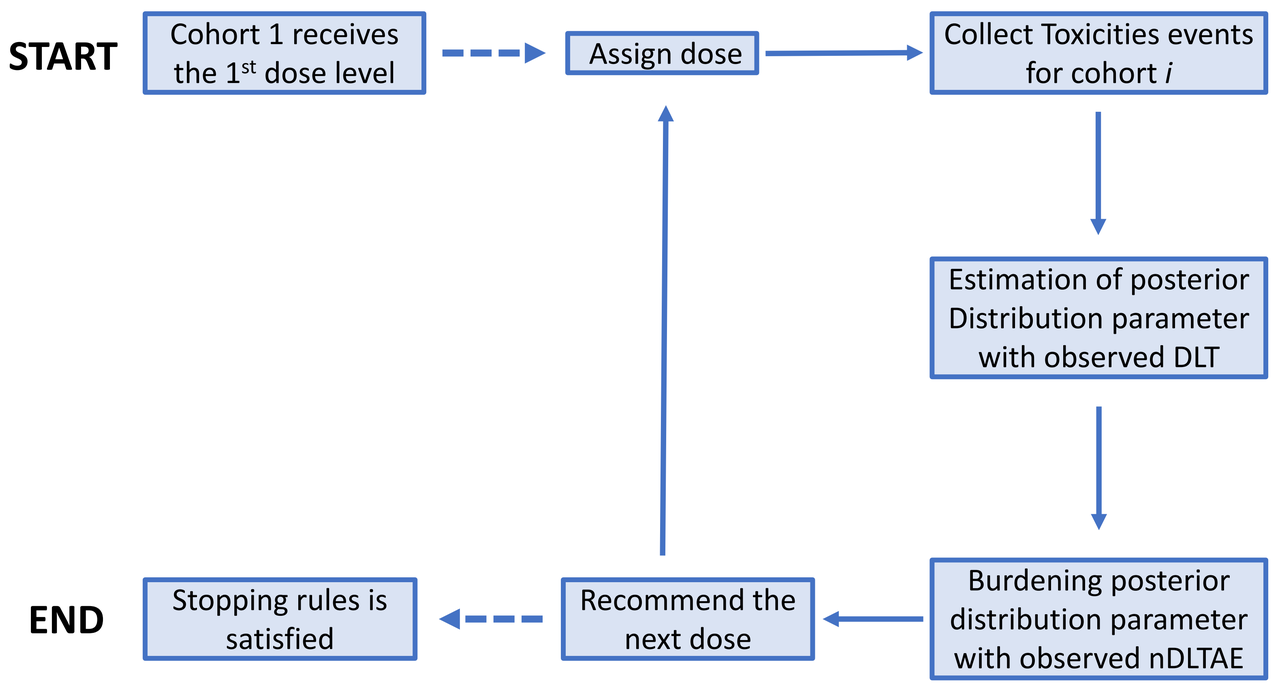
$$log\left(\frac{p}{1-p}\right) = \theta_1 + e^{\theta_2} \cdot log\left(\frac{d}{d_{ref}}\right)$$

Our improvement (**BBLRM**): Additional parameter δ to account for "non-DLT Adverse Events" (nDLTAE) **identified by the clinicians** that although not meeting the definition of DLT, suggesting that higher doses are very likely to result in DLTs.

$$log\left(\frac{p}{1-p}\right) = \theta_1 + |\delta \cdot \theta_1| + e^{\theta_2} \cdot log\left(\frac{d}{d_{ref}}\right)$$

$\boldsymbol{N.B}$: $\boldsymbol{\delta \sim U(a; b)}$ **burdens** the estimated toxicity probability p where the interval $(\boldsymbol{a}; \boldsymbol{b})$ is related to the dose d, proportionally to the nDLTAE observed at that cohort.

Dose-escalation process



To access the full article and get additional information on the method and further simulation results, scan the QR code.

Authors:
Luca Genetti, Associate Biostatistician, Evotec
Andrea Nizzardo, Manager of Clinical Biometry, Evotec

evotec