

AI-Augmented Bayesian Methods for Late-Onset Toxicity in Early-Phase Trials

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Overview

Late-onset Toxicity in Early Phase Clinical Trials

Adaptive and Traditional Dose-Finding
Approaches

Bayesian Simulation Techniques

AI-driven Adaptive Bayesian Models For Late-
onset Toxicities

Conclusions

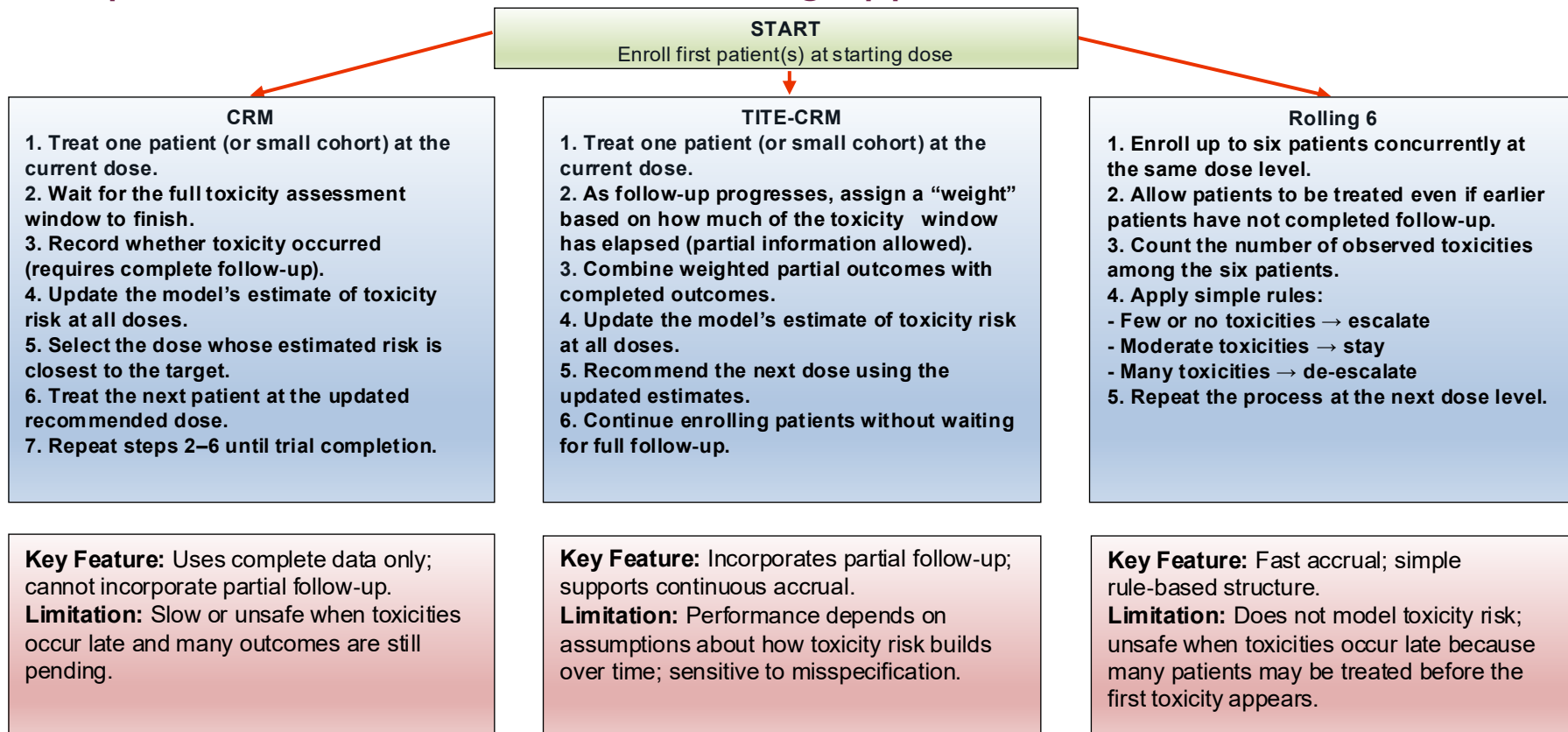
Introduction: Addressing Late-Onset Toxicity in Early-Phase Trials

- Late-onset toxicities remain a major challenge in early-phase trials, particularly with targeted therapies.
- Existing dose-finding designs (CRM, TITE-CRM, Rolling 6) struggle with delayed events, censored data, and fragile model assumptions.
- Bayesian simulation methods using posterior predictive probabilities offer stronger tools for anticipating future toxicity risk.
- Predictive metrics enable proactive safety oversight, including formal stopping rules and accrual suspension.
- Emerging AI-driven adaptive Bayesian models dynamically update parameters to improve prediction accuracy for late-onset toxicities.

What We Investigate in This Work

- We examine how traditional designs (CRM, TITE-CRM, Rolling 6) behave under realistic late-onset toxicity patterns.
- We assess Bayesian simulation techniques that use posterior predictive probabilities to evaluate safety, accrual suspension, and overdose control.
- We compare limitations of current approaches when toxicity is delayed, outcomes are censored, or follow-up is incomplete.
- We explore AI-driven adaptive Bayesian models (BNN, GP hazard models, RL-based dose escalation) that update toxicity predictions dynamically as new partial and full data arrive.

Adaptive and Traditional Dose-Finding Approaches



Bayesian Simulation Techniques

- Uses repeated simulated trials to see how a design performs under real-world conditions like delayed toxicity and partial follow-up.
- Posterior predictive modeling forecasts future toxicities, helping define stopping rules, dose changes, and accrual pauses.
- Clarifies assumptions in CRM, TITE-CRM, and similar designs, showing when they may be too aggressive or too conservative.
- Supports designs such as Joint TITE-CRM and TITE-BOIN12 by evaluating safety and efficacy risks at each interim look.
- Enhances traditional methods by making dose-finding decisions more transparent, calibrated, and safer in the presence of late-onset events.

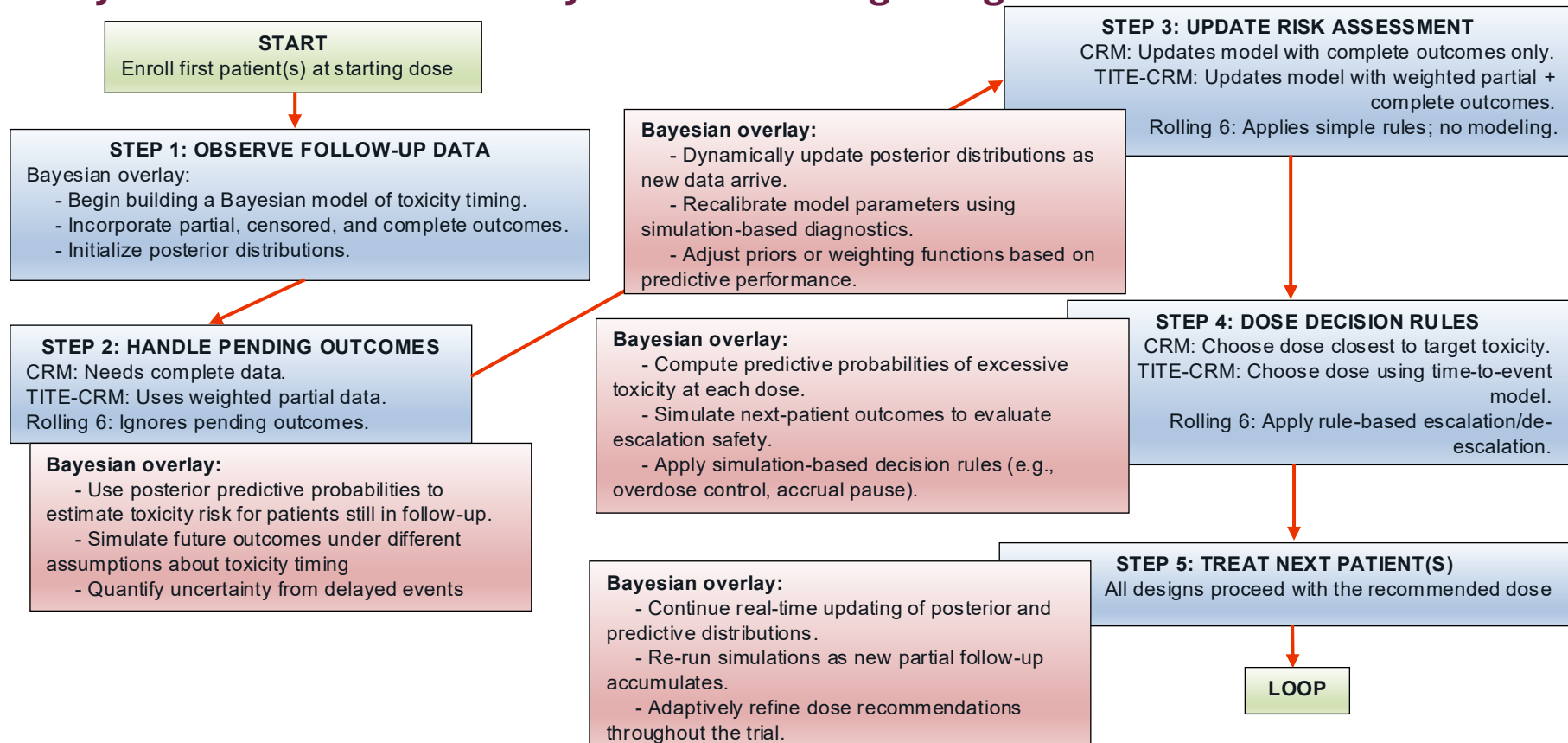
Traditional Designs vs. Bayesian-Enhanced Approaches

Design/ Approach	Core idea	How it handles late-onset toxicity	Role of Bayesian simulation	Typical use case
CRM	Model-based dose-toxicity curve updated as outcomes accrue	Requires mostly complete DLT data; struggles with many pending outcomes	Used to calibrate priors, assess safety, and quantify operating characteristics under delayed events	Early-phase trials with relatively short DLT windows
TITE-CRM	Extends CRM with time-to-event weighting for partial follow-up	Uses weighted partial data; still sensitive to assumptions about risk over time	Simulation evaluates different weighting schemes, accrual patterns, and misspecification scenarios	Trials with multi-cycle or delayed toxicities where model-based design is acceptable
Rolling 6	Rule-based design allowing up to six patients per dose	Does not model time-to-event; vulnerable when toxicities are late	Simulation highlights risks of overdosing and motivates more advanced designs	Pediatric or simple settings with expected early toxicities
Joint TITE-CRM / TITE-BOIN-type designs	Bayesian time-to-event models with predictive decision rules	Explicitly model late-onset toxicity (and often efficacy) over multiple cycles	Simulation central to design: calibrates rules, evaluates safety/efficacy trade-offs, and tunes predictive thresholds	Modern immunotherapy/targeted trials with late-onset safety and activity outcomes

Posterior Predictive Probabilities

- Estimate future toxicity risks using all available data, including partial or censored follow-up.
- Simulate possible outcomes at each dose after updating the Bayesian dose–toxicity model.
- Identify risks such as DLT occurrence, exceeding safety limits, or violating toxicity-control rules.
- Enable real-time decisions in designs like TITE-BOIN12, even when many patients have incomplete follow-up.
- Improve safety in late-onset toxicity settings by accounting for uncertainty in outcomes that have not yet occurred.

Bayesian Simulation Overlay on Dose-finding Designs



Artificial Intelligence (AI)-Driven Adaptive Bayesian Models for Late-onset Toxicities

- Combine machine-learning flexibility with Bayesian updating to handle delayed and censored toxicity data.
- Learn nonlinear, multi-cycle time-to-event patterns that fixed models like TITE-CRM cannot capture.
- Continuously update dose-toxicity estimates as new partial or complete outcomes arrive.
- Improve safety, stability, and decision-making in modern oncology trials with late-onset events.
- Provide a more adaptive and data-responsive framework for early-phase dose finding.

Three AI-Bayesian Approaches & Why They Outperform TITE-CRM

Bayesian Neural Networks (BNN)

- Learns nonlinear toxicity-time patterns using Bayesian neural network weights.
- Continuously updates posterior over weights as partial and full follow-up arrive.
- Captures delayed or heterogeneous toxicity trajectories better than TITE-CRM.

Gaussian Process (GP) Hazard Models

- Places a nonparametric Gaussian Process prior on the hazard function.
- Learns smooth, flexible, possibly multi-phase hazard curves over dose and time.
- Naturally incorporates censored observations and late-onset toxicity.

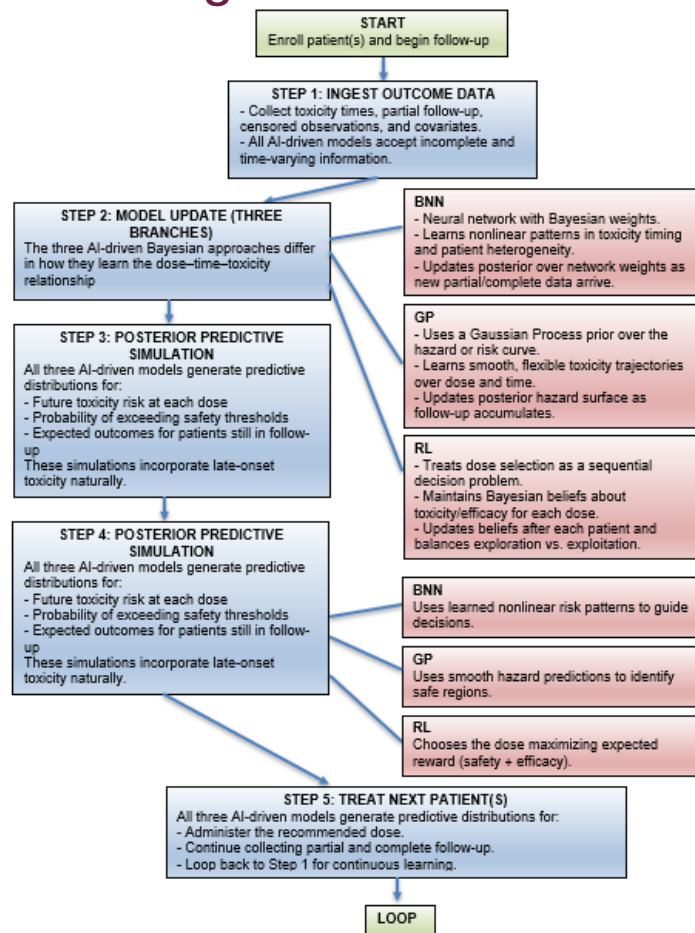
Reinforcement Learning (RL) / Contextual Bandits

- Treats dose escalation as a sequential decision process.
- Maintains Bayesian beliefs about toxicity/effectiveness of each dose.
- Balances exploration vs. exploitation, selecting doses that optimize safety and efficacy.
- Uses posterior predictive probabilities to assess overdose risk for patients still in follow-up.

Key Advantage Over TITE-CRM

- No reliance on fixed hazard structure or predetermined weighting rules.
- Models learn from the data, adapting dynamically as new toxicity times emerge.
- Posterior predictive simulation improves overdose control and safety monitoring under delayed toxicity.

AI-Driven Bayesian Dose-finding Workflow



Conclusions – Challenges & the Role of Bayesian Simulation

- Late-onset and censored toxicities weaken traditional dose-finding methods that rely on fixed timing assumptions.
- CRM, TITE-CRM, and Rolling 6 struggle when toxicity develops across multiple cycles, as seen with modern immunotherapies and targeted agents.
- Bayesian simulation evaluates designs under realistic accrual and follow-up patterns, improving understanding of safety and operating characteristics.
- Posterior predictive probabilities quantify uncertainty and support transparent stopping, escalation, and overdose-control rules.
- These tools strengthen decision-making when many outcomes are still pending.

Conclusions – AI-Driven Bayesian Models & the Path Forward

- AI-adaptive Bayesian models learn the dose–time–toxicity relationship directly from data, capturing nonlinear and delayed patterns.
- Bayesian neural networks and similar tools detect complex hazard shapes that traditional parametric models may miss.
- These models complement—not replace—CRM and TITE-CRM by addressing their sensitivity to timing assumptions and model misspecification.
- Hybrid strategies combining AI, Bayesian simulation, and established designs improve dose selection in long-toxicity-window trials.
- Dynamic updating and predictive modeling create a safer, more transparent framework for early-phase oncology studies.



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Thank you!

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