

Clinical trial simulation to explore AUC-guided vancomycin dosing

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WHAT YOU SHOULD KNOW

- A New Zealand clinical study showed better vancomycin AUC₂₄ target range attainment after Bayesian AUC-guided dosing was introduced, with a 68% lower acute kidney injury hazard (HR 0.32, 95% CI 0.12–0.82).
- Our clinical trial simulation (CTS) reproduced the local clinical study exposure direction: AUC-guided dosing kept AUC₂₄ closer to target, while empirical trough-guided dosing produced broader and higher exposure.
- This CTS extends beyond exposure and target-range endpoints, supporting larger study designs and future patient-outcome projections.

Background

- Vancomycin dosing is traditionally guided by trough based therapeutic drug monitoring (TDM). An Auckland before-after cohort study evaluated a local change from trough-guided TDM to AUC-guided target concentration intervention (TCI) dosing supported by the Bayesian forecasting tool NextDose (Ma, 2022). This clinical study benchmarks CTS development by comparing observed and simulated exposure patterns and guiding future dosing and outcome simulations.

Aims

- To develop a vancomycin CTS framework for the Auckland setting that compares AUC₂₄ exposure and target-window attainment between AUC-guided and empirical trough-guided dosing.

Methods

Data and subjects

- Virtual patients (n=200 per arm) were sampled from a local covariate database (Holford et al., 2024). The CTS framework was implemented in R, NONMEM and Wings for NONMEM.

Shared initial dosing and dose rounding

- Both arms used the same Auckland initial regimen: 25 mg/kg loading dose, then maintenance dosing from the Cockcroft Gault creatinine clearance nomogram. The first concentration was taken before the fourth dose. All simulated doses were rounded to the nearest 250 mg to reflect clinical practice.

Arm 1 — AUC-guided

- After the first concentration review, NextDose generated Bayesian dose recommendations targeting AUC₂₄ = 500 mg·h/L. Target range was defined as AUC₂₄ = 400 to 600 mg·h/L.

Arm 2 — Empirical trough-guided

- After the first concentration review, maintenance doses were adjusted by trough concentration toward 15 to 20 mg/L using local guideline bands. AUC₂₄ target range attainment was evaluated as an exposure benchmark, not as the dosing target.

Execution events

- Delayed doses, missed or withheld doses, and sampling gaps were simulated by review occasion; early cessation was simulated per patient. Event probabilities were informed by Auckland clinical data and compared with clinical benchmarks.

Results

Clinical benchmarking and exposure pattern

- Virtual patient covariates aligned with the Auckland clinical data. Simulated AUC₂₄ reproduced the clinical exposure direction at first and final review (Table 1). Across Bayesian review occasions, the AUC-guided cohort stayed close to the 500 mg·h/L target, while empirical trough-guided dosing produced broader and higher AUC₂₄ exposure (Figure 1). Final distributions narrowed around target with AUC-guided dosing but shifted higher with trough-guided dosing (Figure 2).

Target-window attainment

- AUC-guided dosing improved review-level target-window attainment in both the clinical and CTS cohorts (Table 2). Cumulative first-attainment curves showed earlier and higher patient-level attainment with AUC-guided dosing, while trough-guided dosing remained lower by the final review (Figure 3).

Execution-event context

- Delayed doses, missed or withheld doses, sampling gaps and early treatment cessation were summarized across clinical and CTS cohorts for both dosing strategies. Table 3 compares simulated execution with Auckland observations, supporting interpretation of exposure and target attainment under realistic study conduct.

Table 1. AUC₂₄ exposure at first review and final review. Values are median [5th, 95th percentile], mg·h/L. First review precedes strategy-specific feedback; final review is the 12th review occasion, approximately 7 days after the first dose, after repeated review and dose adjustment.

AUC ₂₄ , mg·h/L [5th, 95th]	Clinical trough-guided arm	Clinical AUC-guided arm	CTS trough-guided arm	CTS AUC-guided arm
First review	555 [305, 741]	550 [306, 766]	576 [391, 863]	576 [391, 863]
Final review	632 [402, 862]	522 [357, 733]	736 [317, 1690]	491 [406, 594]

Table 2. AUC₂₄ target-range attainment used as an exposure benchmark. Values are % (n/N). Time to first attainment is shown in Figure 3.

Endpoint	Clinical trough-guided arm	Clinical AUC-guided arm	CTS trough-guided arm	CTS AUC-guided arm
All review occasions within AUC ₂₄ range	39.4% (384/974)	59.0% (511/866)	24.1% (557/2314)	84.1% (1956/2327)
Patients with ≥1 target-range AUC ₂₄	80.2% (175/218)	93.9% (214/228)	78.0% (156/200)	98.0% (196/200)

Table 3. Execution events by clinical cohort and CTS dosing strategy. Values are % (n/N) except sampling gap. Dose events are per dosing opportunity; early cessation is per patient; sampling gaps are expected sampling or review opportunities without an available concentration result.

Execution event	Clinical Trough-guided arm	Clinical AUC-guided arm	CTS Trough-guided arm	CTS AUC-guided arm
Delayed dose	4.0% (186/4608)	3.6% (219/6006)	2.9% (106/3640)	3.5% (109/3133)
Missed or withheld dose	2.2% (100/4608)	1.5% (93/6006)	3.1% (114/3640)	2.1% (66/3133)
Sampling gap	1.5%	1.0%	0.9%	1.2%
Early treatment cessation	4.4% (9/203)	4.5% (9/200)	4.5% (9/200)	4.0% (8/200)

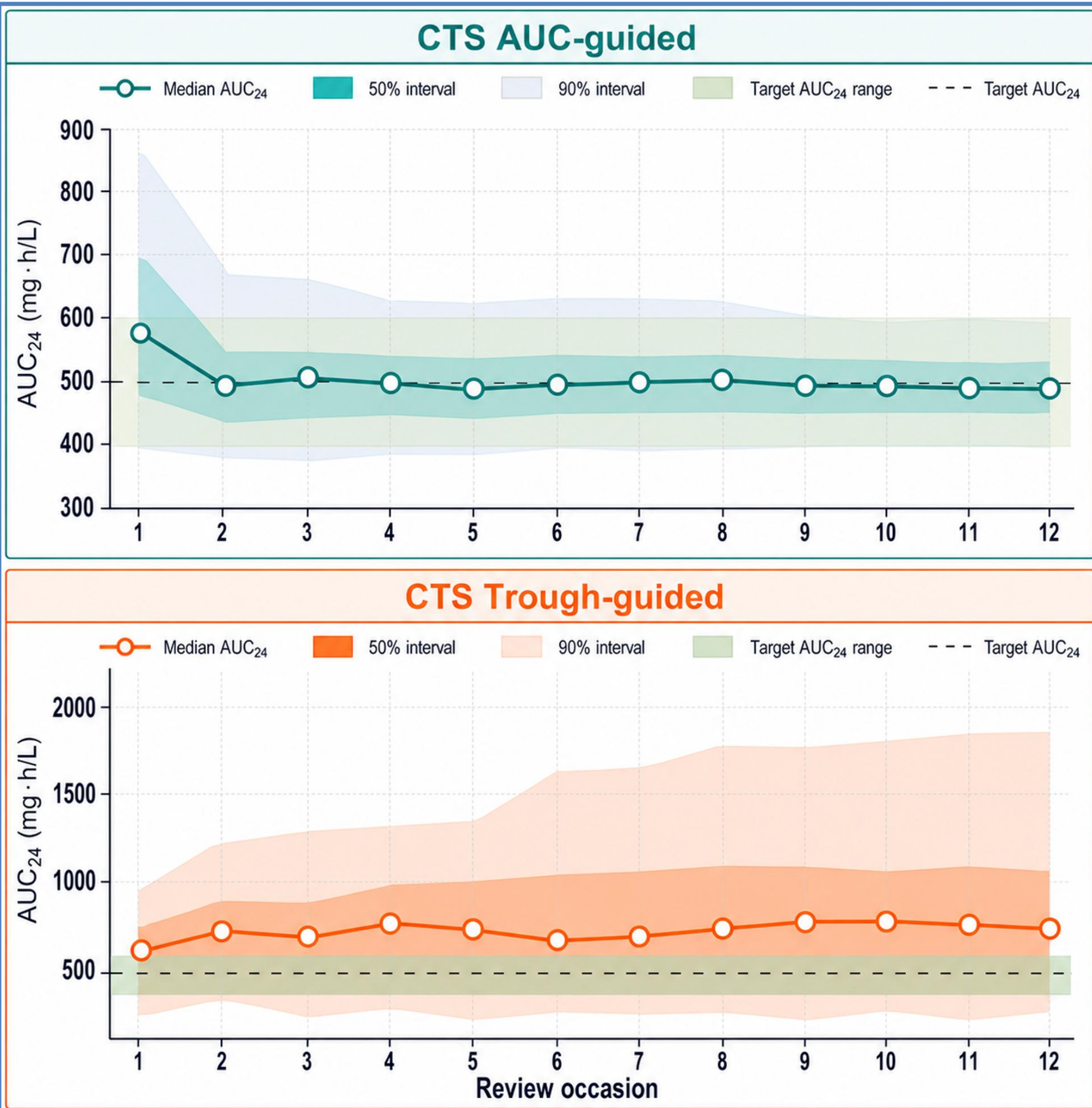


Figure 1. Simulated AUC₂₄ trajectories across review occasions under AUC-guided and empirical trough-guided dosing.

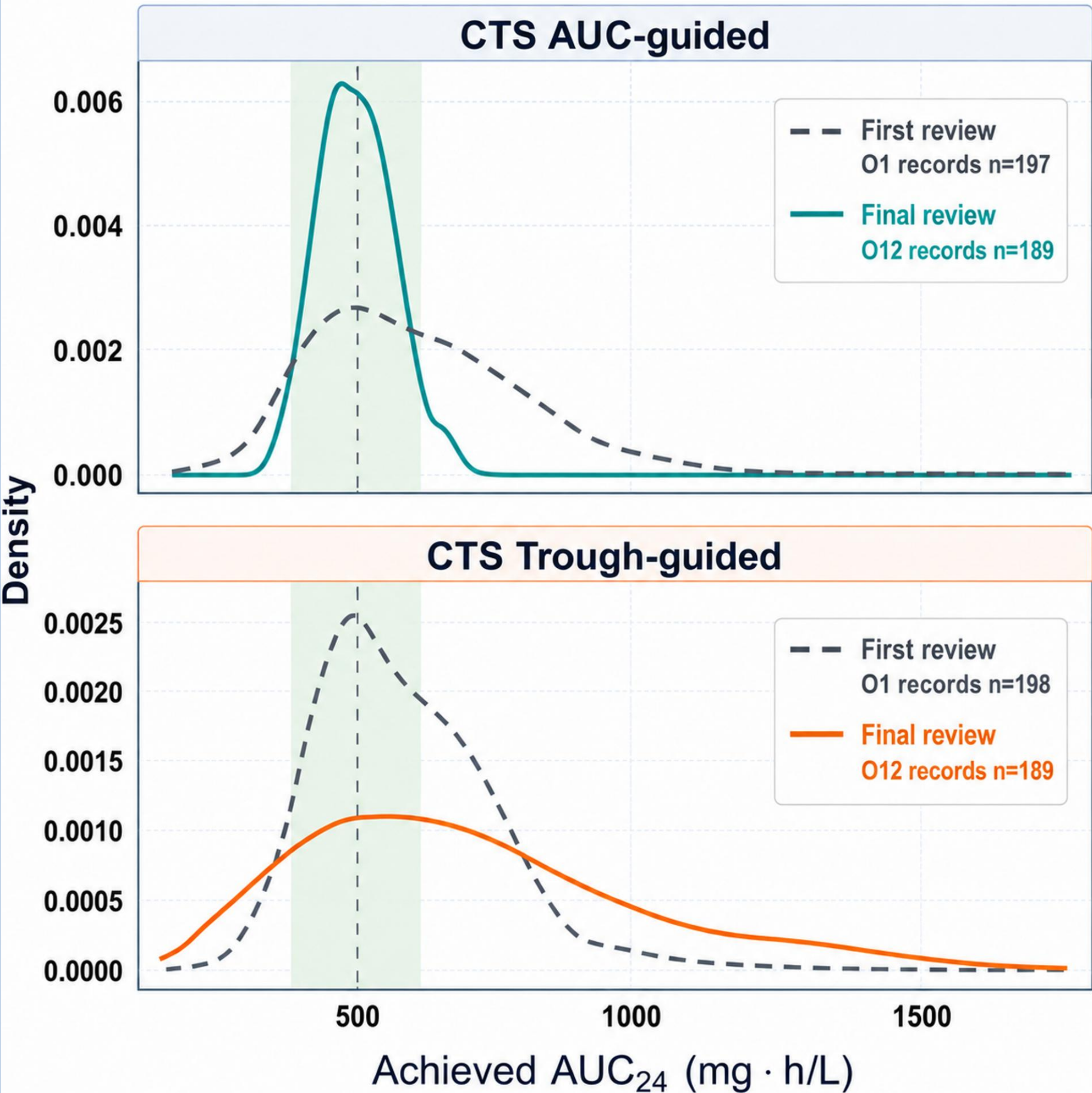


Figure 2. CTS AUC₂₄ distributions at first and final review. Curves use patient-level summaries; O1/O12 labels show available review records after execution events. First review was before feedback and was shared across strategies. AUC-guided dosing narrowed final exposure around target, while trough-guided dosing remained broader and higher.

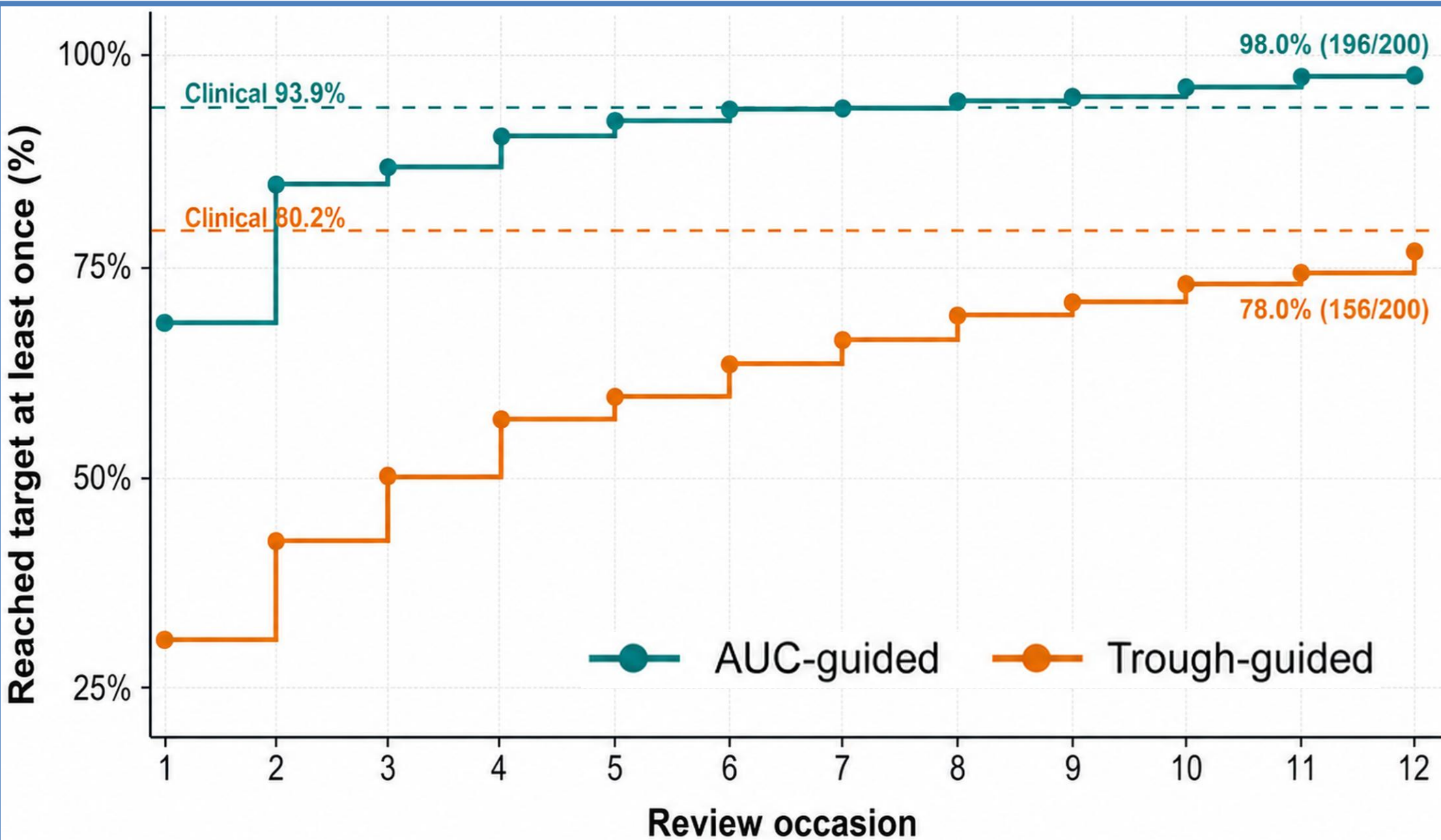


Figure 3. Cumulative proportion of patients reaching the AUC₂₄ target range at least once over 12 review occasions (~7 days). Dashed lines show clinical cohort references; solid step curves show CTS patient-level first attainment.

Conclusion

The CTS reproduced key Auckland clinical benchmarks, including covariates, AUC₂₄ exposure features and execution events, supporting its use as a locally grounded simulation framework. Within the simulated cohorts, AUC-guided dosing moved AUC₂₄ toward the 500 mg·h/L target and produced tighter final distributions, whereas empirical trough-guided dosing remained broader, shifted higher and achieved lower final target-window attainment. By retaining dosing, sampling and early treatment cessation as explicit outputs, this framework provides a practical platform for testing local dosing and sampling strategies, with future extensions to special populations, health-economic evaluation and patient-outcome projections.

REFERENCES

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COMPUTATION

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