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Enhancing Long-Term Cost-Effectiveness Projections Using Real-World Evidence-Informed Uncertainty Analysis

EE523

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TheoRlytics

INTRODUCTION

- Cost-effectiveness analyses (CEAs) for chronic diseases often rely on clinical trial data with limited follow-up durations and long-term projections of survival, costs, and health outcomes require extrapolation beyond observed trial data[1,2]
- Such extrapolation introduces significant uncertainty, potentially impacting decision confidence. Hence, Probabilistic sensitivity analysis (PSA) is commonly used to quantify uncertainty, but it often applies simplified assumptions[1]
- Incorporating real-world evidence (RWE) on long-term outcomes offers a practical approach to reduce uncertainty and improve the robustness of CEAs[2,3]
- The integration of RWE into economic models can improve the credibility and relevance of CEAs[3]

OBJECTIVE

- To identify and apply practical methods for integrating long-term real-world outcome data into the PSA framework of chronic disease CEAs
- To evaluate the impact of RWE integration on reducing extrapolation uncertainty and improving the reliability of cost-effectiveness estimates

METHODS

- A simulation-based PSA framework was developed to compare:
  - **Trial-only scenario:** Parameter uncertainty informed solely by clinical trial data
  - **RWE-informed scenario:** Trial evidence updated using long-term RWE through Bayesian updating
- Analyses were conducted in R (version 4.3.5), and a Monte Carlo simulation with 1,000 iterations was conducted for each scenario to capture parameter uncertainty
- Key clinical, survival, and economic input parameters used to populate the PSA model under both the trial-only and RWE-informed scenarios are summarized in **(Table 1)**

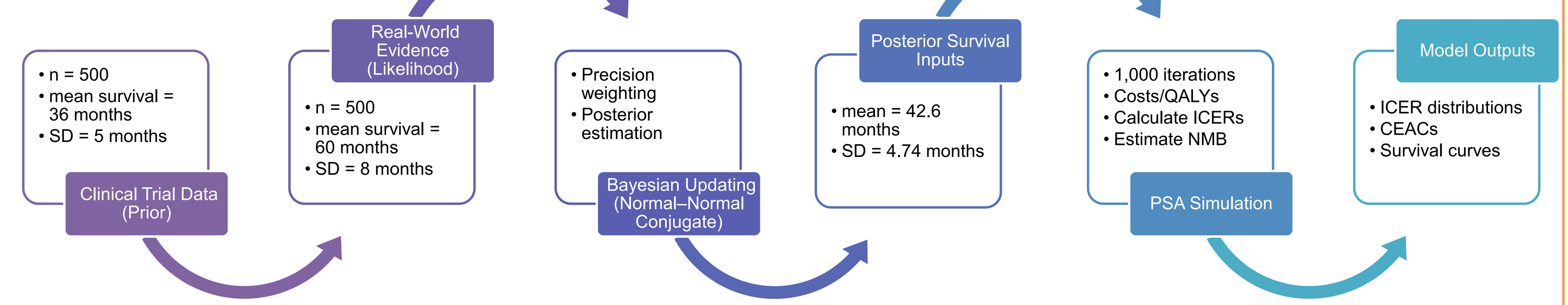
Table 1: Key Model Inputs and PSA Parameters

Parameter Category	Trial-Only Scenario	RWE-Informed Scenario
Trial cohort size	500	500
RWE cohort size	—	500
Mean survival (months)	36.0	42.74 (posterior)
Survival SD	5.0	4.24
Mean costs (USD)	50,000	52,000
Cost SD (USD)	8,000	7,000
Mean QALYs	4.0	4.5
QALY SD	0.5	0.45
PSA iterations	1,000	1,000
WTP range	0–100,000/QALY	0–100,000/QAL

PSA: Probabilistic Sensitivity Analysis; QALY: Quality-Adjusted Life Year; RWE: Real-World Evidence; SD: Standard Deviation; USD: United States Dollar; WTP: Willingness To Pay

- RWE integration was implemented using a Bayesian Normal-Normal conjugate update. Trial data were treated as the prior distribution and RWE as the likelihood
- Precision weights were calculated, and posterior variance/ posterior mean were estimated
- The posterior distribution replaced the trial-only survival distribution in the RWE-informed PSA scenario
- Costs and QALYs were sampled independently from normal distributions using scenario-specific parameters, and incremental cost-effectiveness ratios (ICERs) were calculated for each PSA iteration
- Cost-effectiveness acceptability curves (CEACs) were generated across willingness-to-pay (WTP) thresholds
- The overall analytical workflow illustrating the integration of clinical trial data and real-world evidence within the Bayesian PSA framework is presented in Figure 1

Figure 1: Overview of Bayesian RWE Integration within PSA Framework



SD: Standard Deviation

RESULTS

- Bayesian updating of survival data yielded a posterior mean survival of 42.74 months (SD = 4.24), positioned between the trial-only and RWE-only estimates
- Integration of RWE reduced parameter uncertainty in long-term survival extrapolations compared with estimates derived solely from trial data
- The mean ICER decreased from USD 12,608 in the trial-only scenario to USD 11,608 following RWE integration, and the 95% uncertainty interval for the ICER narrowed from USD 8,016-18,619 to USD 8,066-15,873 (Table 2)
- At a WTP threshold of USD 15,000 per QALY gained, the probability of cost-effectiveness increased from 83.6% to 95.1% following incorporation of RWE (Table 2)

Table 2: PSA Numeric Summaries - Costs, QALYs, and ICERs Across Scenarios

Parameter	Without RWE Mean (95% CI)	With RWE Mean (95% CI)	Absolute Change	CI Width Reduction
Total Costs (USD)	50,067 (35,051 – 64,664)	52,465 (38,998 - 67,031)	+2,398	—
QALYs	4.01 (3.06 – 4.98)	4.53 (3.65 - 5.41)	+0.52	—
ICER (USD / QALY)	12,608 (8,016 – 18,619)	11,608 (8,066 – 15,873)	−1,000	▼ 26.4%
CEAC @ WTP USD 10,000	14.4%	19.9%	+5.5	—
CEAC @ WTP USD 12,000	44.4%	59.7%	+15.3	—
CEAC @ WTP USD 15,000	83.6%	95.1%	+11.5	—

CEAC: Cost-Effectiveness Acceptability Curve; ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted Life Year; RWE: Real-World Evidence; USD: United States Dollar; WTP: Willingness To Pay

- Incorporating long-term RWE via Bayesian updating shifted the mean survival estimate from 35.8 to 42.6 months - a gain of 6.8 months, producing a survival curve that better reflects real-world patient trajectories than trial data alone **(Figure 2)**
- This upward shift in survival directly translates to higher projected QALYs in the economic model, narrowing the ICER and improving the probability of cost-effectiveness across all WTP thresholds
- CEAC analysis demonstrated consistently higher probabilities of cost-effectiveness across all evaluated WTP thresholds in the RWE-integrated scenario, as shown in **(Figure 3)**

Figure 2: Survival curves for trial-only, RWE-only, and Bayesian-updated posterior estimates

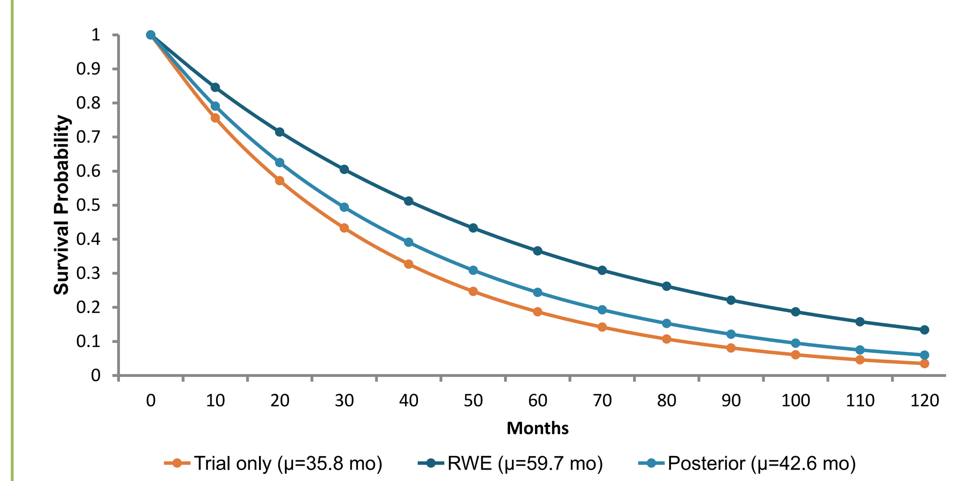
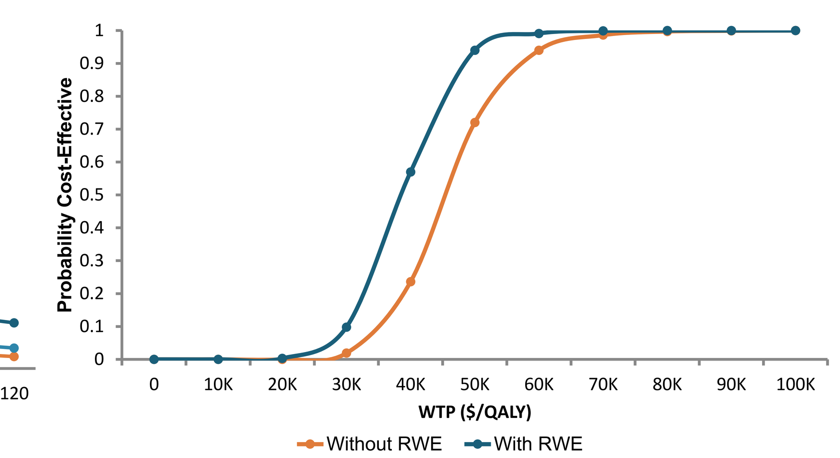


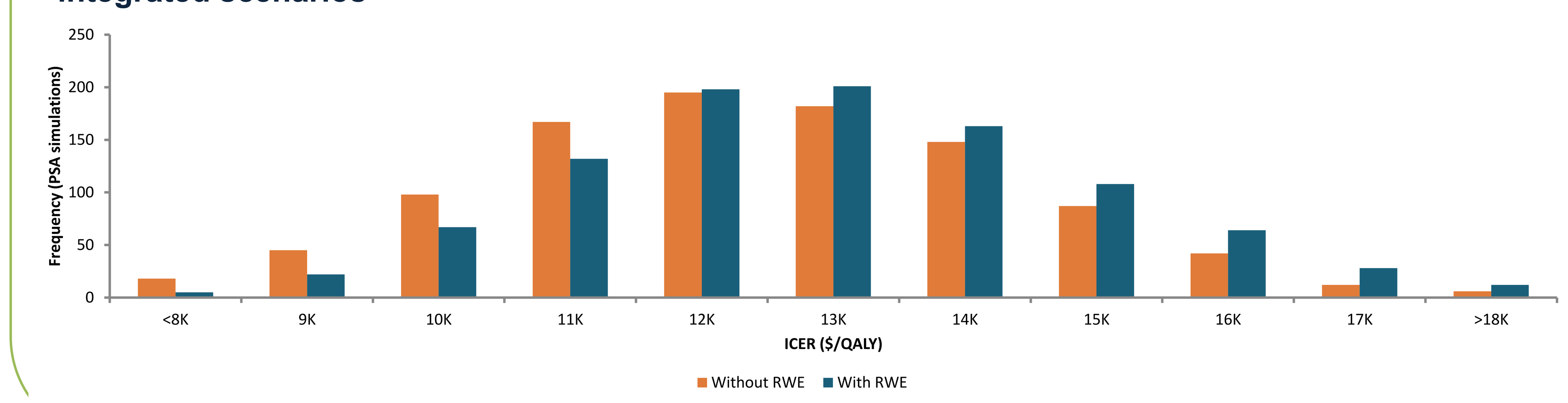
Figure 3: CEACs for trial-only and RWE-integrated scenarios



CEAC: Cost-Effectiveness Acceptability Curve; QALY: Quality-Adjusted Life Year; RWE: Real-World Evidence; WTP: Willingness To Pay

- Across 1,000 PSA simulations, the RWE informed model produced a tighter, more concentrated ICER distribution compared to the trial-only approach, with fewer simulations falling in extreme low or high-cost ranges **(Figure 4)**
- The mean ICER reduced from $12,608 to $11,608 per QALY gained when RWE was incorporated, and the 95% credible interval narrowed by over a quarter, directly reducing decision uncertainty at standard WTP thresholds

Figure 4: Distribution of incremental cost-effectiveness ratios (ICERs) in trial-only and RWE-integrated scenarios



ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted Life Year; RWE: Real-World Evidence

LIMITATIONS

- The survival and cost inputs used in this analysis are simulated and not derived from a specific disease area or treatment; findings should be interpreted as a methodological demonstration rather than a clinical or policy recommendation
- The Bayesian Normal-Normal conjugate update assumes that both the trial and RWE survival data follow a normal distribution; in practice, survival data are often right-skewed and may require alternative updating frameworks such as log-normal or Weibull-based approaches
- Survival was extrapolated using an exponential function for illustrative clarity; real-world HTA submissions typically evaluate multiple parametric forms and select the best-fitting model based on statistical and clinical criteria

CONCLUSION

- Integration of long-term RWE into PSA meaningfully reduces uncertainty in extrapolated CEAs for chronic diseases. The application of Bayesian updating provides a transparent and methodologically robust approach for combining trial and RWE-derived survival estimates
- Incorporating RWE led to narrower distributions of ICERs, higher probabilities of cost-effectiveness across WTP thresholds, and enhanced decision-making confidence. These findings highlight the value of leveraging RWE to improve the validity, credibility, and policy relevance of long-term economic evaluations in healthcare
- Standardized methodology for integrating RWE into PSA frameworks including agreed criteria for data source eligibility, updating procedures, and sensitivity testing would strengthen consistency and reproducibility of long-term cost-effectiveness evidence across HTA submissions globally

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Disclosure:
PB, AS, NT, RR, and SP, the authors declare that they have no conflict of interest