Incorporating Real-World Evidence into Time-to-Event Extrapolations from Clinical Trial Data

MSR171

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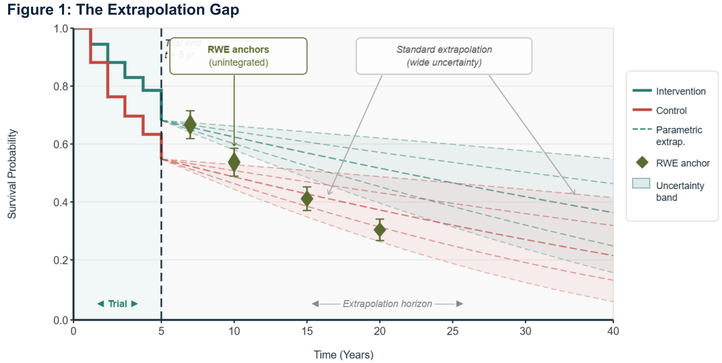
INTRODUCTION

- Health technology assessment submissions routinely require survival extrapolation to a lifetime horizon; parametric models selected by AIC/BIC remain the operational standard, yet introduce substantial uncertainty beyond trial follow-up of 3-7 years[1]
- Real-world evidence (RWE) from registries, electronic health records, and published landmark analyses increasingly provides survival estimates at longer time horizons. However, no formal mathematical framework exists to bridge these data sources with trial-based parametric extrapolations[2]

Figure 1: The Extrapolation Gap



- Model averaging approaches (Jackson et al.[2]; Yin & Ibrahim[4]) reduce single-model reliance but operate purely within the trial data space - RWE anchor points remain external and subjectively interpreted by analysts[3]
- This methodological gap is most consequential for rare disease and novel oncology submissions, where limited trial follow-up coincides with the highest long-term uncertainty and greatest influence of extrapolation assumptions on ICER estimates[4]

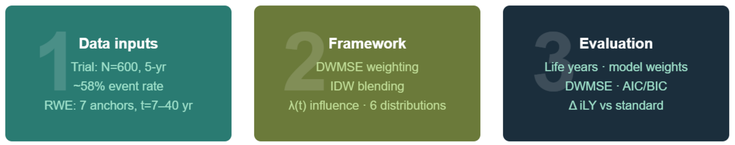
OBJECTIVE

- To develop and validate a methodological framework for integrating RWE anchor points into parametric survival extrapolations using distance-weighted model averaging and inverse distance-weighted blending
- The impact on life-year estimates, model selection, and incremental treatment benefit was quantified relative to standard AIC-weighted extrapolation, applied to a simulated 5-year trial with external survival evidence to 40 years

METHODS

Phase 1 - Simulation Design

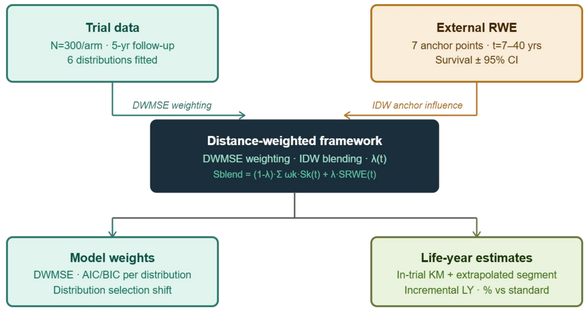
- Two-arm trial simulated (N=300/arm; 1:1 allocation) with Weibull event generation: intervention (shape=1.5, scale=9) and control (shape=1.2, scale=6); random censoring Uniform[3,7] years; trial cutoff at 5 years
- Six parametric distributions were fitted independently per arm via maximum likelihood: Exponential, Weibull, Log-Normal, Log-Logistic, Gompertz, and Generalized Gamma
- External RWE was defined as 7 time-survival pairs (t=7,10,15,20,25,30,40 years) with associated standard errors, representing registry-sourced survival anchors
- Kaplan-Meier estimates were preserved verbatim within the trial period; framework applied exclusively to the extrapolation segment (t>5 years)



Phase 2 - Distance-Weighted MSE Model Weighting

- For each parametric distribution k, DWMSE was computed against RWE anchor points with temporal proximity weighting - anchors closer to trial end carry higher weight
- Model weights were derived as normalized inverse DWMSE: distributions with better fit to external evidence receive proportionally higher weight
- Standard comparator: Akaike weights (AIC-based), representing conventional model averaging with no RWE influence

Figure 2: Overall framework



Phase 3 - Inverse Distance-Weighted Blending

- At each extrapolation time point, a Gaussian influence function λ(t) governs RWE contribution - zero at trial end, peaking mid-extrapolation (t~15 years), then decaying
- Blended survival was computed as weighted combination of parametric model average and IDW-interpolated RWE surface
- Blending preserves mathematical continuity with KM at trial end while allowing controlled, graduated RWE influence beyond it

Phase 4 - Life-Year Estimation

- Total life years were computed via trapezoidal integration over combined in-trial KM and extrapolated blended survival curve
- Estimated separately for both arms under standard (AIC-weighted) and RWE-integrated approaches
- Incremental life-year difference and percentage impact were quantified as primary comparison metrics

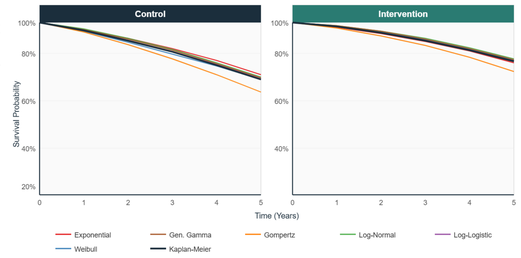
Table 1: Model Weights

Distribution	AIC (Int)	AIC Wt % (Int)	AIC Wt % (Ctrl)	DWMSE (Int)	DWMSE (Ctrl)	RWE Wt % (Int)	RWE Wt % (Ctrl)
Exponential	676.9	0.0	0.4	0.0107	0.0421	47.6	21.8
Weibull	660.7	46.0	15.2	0.0547	0.0691	9.3	13.4
Log-Normal	664.5	28.9	19.7	0.0206	0.0345	24.7	26.7
Log-Logistic	NA	0.0	0.0	NA	NA	0.0	0.0
Gompertz	667.2	3.9	0.1	0.1060	0.0784	4.8	8.6
Gen. Gamma	659.4	21.1	64.6	0.0183	0.0298	13.6	29.5

RESULTS

- All six distributions tracked the Kaplan-Meier closely within the 5-year trial period with minimal divergence, confirming in-trial fit alone is insufficient to discriminate between models for long-horizon projection
- Log-Logistic failed to converge in both arms and was excluded from model averaging
- Under AIC-based weighting, Weibull dominated the intervention arm (46.0%), followed by Log-Normal (28.9%) and Gen. Gamma (21.1%)

Figure 3: Parametric Distributions Fitted to Trial KM Data



- RWE-based weighting reversed this preference entirely - Exponential became dominant (47.6%) with Log-Normal second (24.7%), driven by better alignment with external survival anchors at distant time points
- In the control arm, Gen. Gamma dominated AIC selection (64.6%) but shared weight more evenly under RWE (29.5%), with Exponential rising to 21.8%
- λ(t) rose from zero at trial end, peaked at ~72% around t=13-15 years, and remained above 45% through t=40 - ensuring sustained RWE influence without fully overriding parametric structure
- RWE-integrated curves aligned closely with external anchor points across both arms; the standard AIC-weighted approach diverged substantially beyond t=10, particularly in the control arm
- The separation between standard and RWE-integrated curves was consistent across both arms, reflecting systematic upward revision of long-term survival estimates

Table 2: Life-Year Estimates

Scenario	LY - Intervention	LY - Control	Incremental LY	Δ vs Standard
Standard (AIC-Weighted)	14.29	10.15	4.14	Reference
RWE-Integrated	15.85	11.24	4.61	+11.4%

- RWE integration increased incremental life-year benefit by 11.4% (4.14 → 4.61 years), a difference material to reimbursement decisions at standard HTA thresholds
- Both arms showed proportionally similar upward revision, preserving relative treatment effect structure while improving absolute plausibility of long-term projections

Figure 4: RWE Influence Function λ(t)

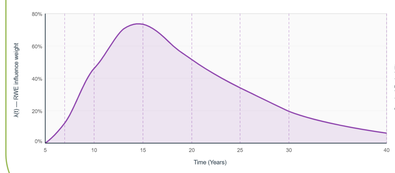
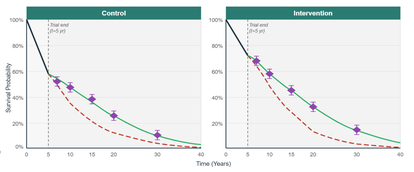


Figure 5: Long-Term Survival Extrapolations



CONCLUSION

- Integration of RWE into parametric survival extrapolations via distance-weighted model averaging materially impacts life-year estimates - an 11.4% increase in incremental benefit (4.14 → 4.61 years) is decision-relevant at standard HTA thresholds including NICE, CADTH, and EU-HTA
- DWMSE-based model weighting provides a transparent, auditable mechanism to favor distributions consistent with external evidence, replacing analyst subjectivity with a data-driven selection criterion - Weibull dominance under AIC was displaced by Exponential under RWE weighting, demonstrating that standard goodness-of-fit metrics alone are insufficient for long-horizon projection
- The IDW blending mechanism with Gaussian λ(t) influence preserves Kaplan-Meier fidelity within the trial period while allowing controlled, graduated RWE influence in extrapolation - peaking at ~72% around t=13-15 years and remaining mathematically continuous throughout
- This framework has direct applicability to novel therapy submissions with limited follow-up but available registry or observational evidence - precisely the scenario most common in rare disease and early-access oncology HTA

References

1. NICE Decision Support Unit. NICE DSU Technical Support Document 14: Survival Analysis for Economic Evaluations Alongside Clinical Trials. 2014.
2. Jackson C, Stevens J, Ren S, et al. Extrapolating survival from randomized trials using external data: a review of methods. Medical Decision Making. 2017;37(4):377–390.
3. Latimer NR. Survival analysis for economic evaluations alongside clinical trials — extrapolation with patient-level data. Medical Decision Making. 2013;33(6):743–754.
4. Yin G, Ibrahim JG. Cure rate models: a unified approach. Canadian Journal of Statistics. 2005;33(4):559–570.
5. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Medical Research Methodology. 2012;12:9.

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Disclosure:
Authors (SP, RR, SM, BS, and AS) declare that they have no conflicts of interest

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