Approaches and Challenges in the Rapid Estimation of Quality-Adjusted Life Expectancy Shortfalls Based on Published Kaplan-Meier Curves and Utility Values

Pollock RF[1], Brown T[1]
[1] Covalence Research Ltd, Harpenden, UK

COVALENCE RESEARCH

Background and Aims

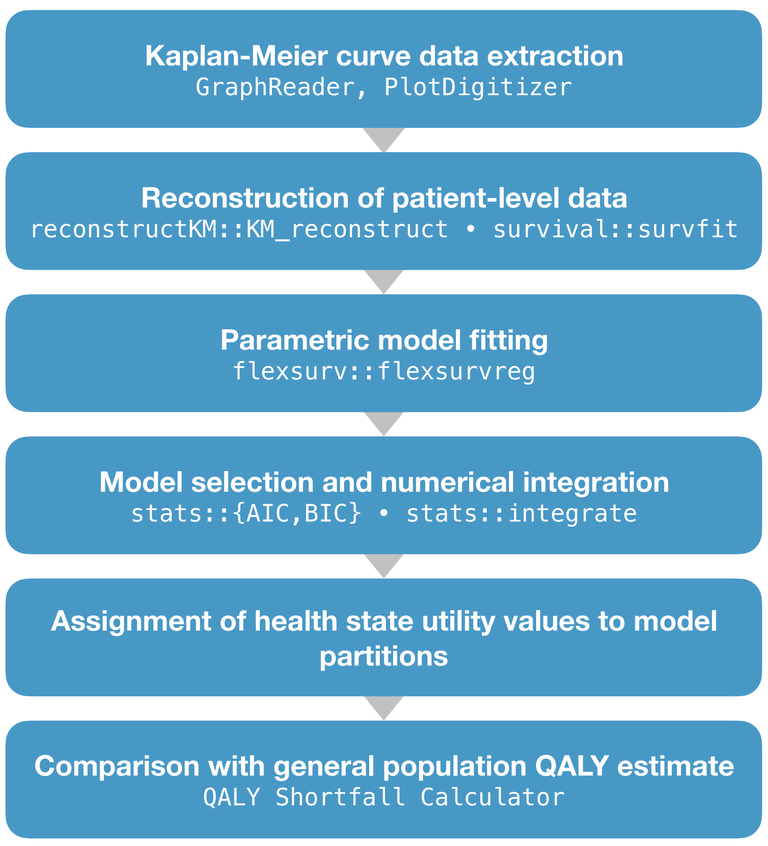
As of 2022, when appraising new healthcare technologies, the UK National Institute for Health and Care Excellence (NICE) considers the severity of the treated condition, regardless of whether or not patients are near end-of-life.[1] Quantitatively, this is achieved through disease severity modifiers which adjust quality-adjusted life expectancy calculations for technologies that treat severe disease. The severity modifier approach was introduced in 2022 to replace the previous modifier that only applied to technologies intended to treat end-of-life conditions. In September 2024, NICE reported that 19 appraisals had used the updated severity weighting, 16 of which resulted in a positive recommendation.[2]

The modifier is determined based on either an absolute or proportional quality-adjusted life year (QALY) shortfall, calculated using the lifetime difference in QALYs between patients with the condition and the general population. When the modifier is used in the economic modelling that forms the basis of a company submission to NICE, its use must be justified in Section 3.6 of the submission. This should include the source of the general population EQ-5D and survival data, and supporting evidence and validation of the calculations must be presented.

There are, however, other situations in which a rapid estimation of eligibilty for the severity modifier may be necessary, not as the basis of the economic modelling in the company submission but, for example, to establish if emerging data from registries or may contradict the evidence in the company submission with regard to eligibility for the severity modifiers as, for example, the quality of best supportive care improves over time.

In the present study, a framework for rapidly estimating the QALY shortfall based on minimal study summary data was developed using a combination of published tools and methodologies.

Figure 1: Flow diagram of QALY shortfall estimation



Methods

The framework (Figure 1) was developed in the context of estimating a QALY shortfall using published Kaplan-Meier curves (OS) from people living with treatment-refractory metastatic colorectal cancer (mCRC) and a published mean health state utility value (HSUV).

Kaplan-Meier curves of OS and were digitised using PlotDigitizer and numbers at risk were extracted from the placebo arm of the RECOURSE trial of TAS-102 in refractory mCRC.[3] The Guyot *et al.* methodology was employed to reconstruct the Kaplan-Meier data (Figure 2) using the `reconstructKM` package in R.[4] Parametric survival models were then fitted by maximum likelihood estimation using the `survfit` package in R and ranked based on goodness-of-fit criteria (Akaike Information Criterion and Bayesian Information Critierion; Figure 3).

Rather than implementing a "full" partitioned survival model in R or Microsoft Excel, integrands were programmed for each of the parametric survival models and used to calculate area under the curve (AUC) by numerical integration. Where necessary, regularisation methods were employed to overcome limitations of survival distributions with long tails and/or divergent integrals.

An HSUV of 0.53 (taken from a systematic literature review of oncology HSUVs) was then applied to the living partition derived from the best fitting survival model.[5] Results were compared with McNamara *et al.* general population QALY estimates using an online QALY shortfall calculator.[6]

Figure 2: Reconstructed Kaplan-Meier data from the placebo arm of the RECOURSE randomised trial

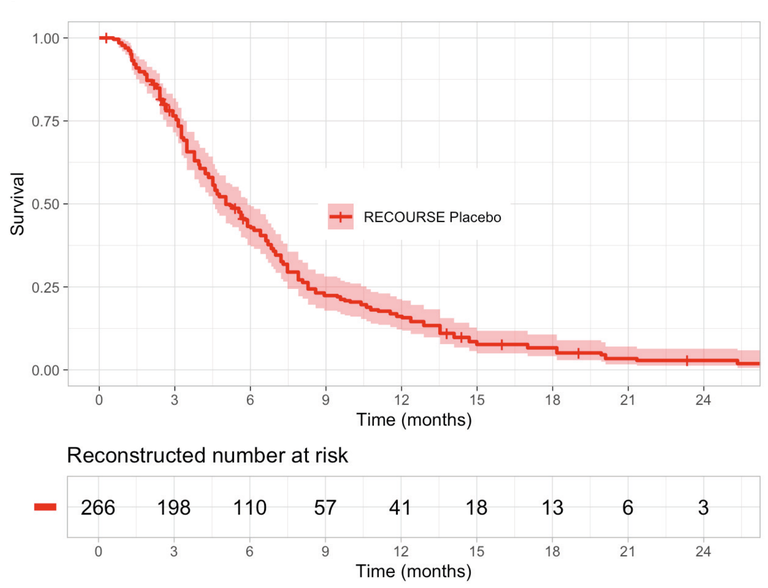
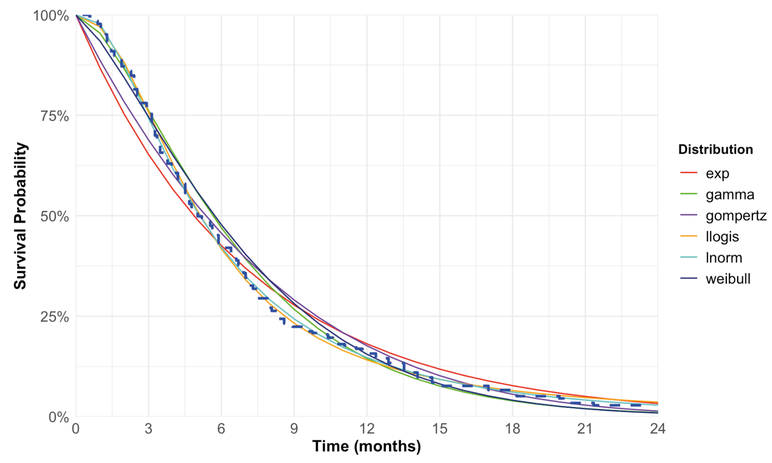


Figure 3: Parametric survival model fits to the reconstructed patient-level survival data from the placebo arm of the RECOURSE randomised trial



Results

The framework facilitated the rapid estimation of the QALY shortfall in patients with treatment-refractory mCRC in the UK based on published Kaplan-Meier curves and HSUVs.

People in the placebo arm of the RECOURSE trial were an average of 61.5 years old at baseline and 38% of the population were female.[7] The lognormal distribution was the best fitting model to the OS data and total AUC was 0.61 years. Applying the literature-derived utility estimate to the partition suggested that patients would experience a further 0.32 QALYs over their remaining life. This compared to 18.10 QALYs in the general age- and sex-matched population based on the QALY shortfall calculator reference case, resulting in an absolute shortfall of 17.78 QALYs and a proportional shortfall of 98.2%. The population would therefore qualify for the 1.7x severity modifier on the basis of the proportional shortfall.

Discussion

Calculations supporting the use of a NICE disease severity modifier must ultimately be as robust as those underpinning the health economic model submitted to NICE; however, in many circumstances, it is useful to rapidly understand the likelihood of a severity modifier being accepted by NICE based on early clinical data or emerging registry data.

The expedited approach presented here has a number of limitations relative to the development of a full partitioned survival model. Most notably in this instance, the model made use of a single living partition as the basis of the QALY estimation, although the approach would easily be extended to include pre- and post-progression partitions or on- and off-treatment partitions, for example. The framework would also not perform well in situations where more sophisticated analyses are required to elicit realistic survival estimates from the Kaplan-Meier curves; for instance, if a high proportion of patients crossed over to an active comparator arm, more complex approaches such as two-stage estimation or rank-preserving structural failure time models would need to be specified to adjust the survival estimates appropriately.

Despite the limitations, the present framework takes an important step towards accelerating the process of QALY shortfall estimation for health technologies whose cost-effectiveness can be evaluated using partitioned survival models.

References

1. NICE. NICE health technology evaluations: the manual. 2022. Available from: https://www.nice.org.uk/process/pmg36
2. NICE. Review of the implementation of the severity modifier. 2024. Available from: https://www.nice.org.uk/Media/Default/Get-involved/Meetings-In-Public/Public-board-meetings/sept-24-pbm-annual-equality-report-board-cover-paper.docx
3. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, Sobrero A, Boucher E, Peeters M, Tran B, Lenz HJ, Zaniboni A, Hochster H, Cleary JM, Prenen H, Benedetti F, Mizuguchi H, Makris L, Ito M, Ohtsu A; RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372(20):1909-19.
4. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9
5. Pourrahmat MM, Kim A, Kansal AR, Hux M, Pushkarna D, Fazeli MS, Chung KC. Health state utility values by cancer stage: a systematic literature review. Eur J Health Econ. 2021;22(8):1275-1288.
6. McNamara S, Schneider PP, Love-Koh J, Doran T, Gutacker N. Quality-Adjusted Life Expectancy Norms for the English Population. Value Health. 2023;26(2):163-169.
7. Study of TAS-102 in Patients With Metastatic Colorectal Cancer Refractory to Standard Chemotherapies (RECOURSE). Available from: https://clinicaltrials.gov/study/NCT01607957?tab=results

Presented at **ISPOR Europe 2024** • Poster HTA76 • Barcelona, Spain • November 17–20, 2024