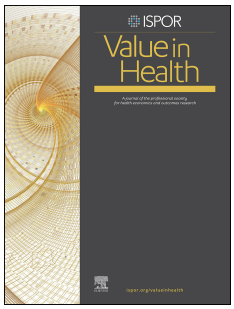

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Unblinded title page

Dynamic Mortality Modelling: Incorporating Predictions of Future General Population Mortality into Cost-Effectiveness Analysis

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Precis: The application of a dynamic approach to mortality modelling is technically simple and has the potential to meaningfully impact estimates of cost-effectiveness analysis.

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Abstract

Objectives: Health economic models commonly apply observed general population mortality rates to simulate future deaths in a cohort. This is potentially problematic, as mortality statistics are records of the past, not predictions of the future. We propose a new dynamic general population mortality modelling approach which enables analysts to implement predictions of future changes in mortality rates. The potential implications moving from a conventional static approach to a dynamic approach is illustrated using a case-study. **Methods:** The model utilised in NICE appraisal TA559, axi-cel for diffuse large B-cell lymphoma, was replicated. National mortality projections were taken from the UK Office for National Statistics. Mortality rates by age and sex were updated each modelled year with the first modelled year using 2022 rates, the second modelled year 2023 and so on. Four different assumptions were made around age distribution: fixed mean age; lognormal, normal and gamma. The dynamic model outcomes were compared to those from a conventional static approach. **Results:** Including dynamic calculations increased the undiscounted life years attributed to general population mortality by 2.4–3.3 years. This led to an increase in discounted incremental life years within the case study of 0.38–0.45 years (8.1–8.9%), and a commensurate impact on the economically justifiable price of £14,456–£17,097. **Conclusions:** The application of a dynamic approach is technically simple and has the potential to meaningfully impact estimates of cost-effectiveness analysis. As a result, we call on health economists and HTA bodies to move towards use of dynamic mortality modelling in future.

Key words: dynamic, mortality, simulation, cost-effectiveness, dynamic mortality modelling, CAR-T, survival, extrapolation

Highlights

1. Health economic models commonly apply observed general population mortality rates to simulate future deaths in a cohort. This is potentially problematic, as mortality statistics are records of the past, not predictions of the future

2.We propose a new dynamic general population mortality modelling approach which enables analysts to implement predictions of future changes in mortality rates. We demonstrate the potential impact of this approach using a replication of the axi-cel model from NICE appraisal TA559

3. Including dynamic calculations increased the undiscounted life years attributed to general population mortality by 2.4–3.3 years with a potentially meaningful impact on the economically justifiable price of £14,456–£17,097

Introduction

In health economic models, general population mortality statistics are commonly used to predict the survival of patients with non-terminal conditions. Typically, this is achieved by identifying age-specific mortality rates from recent population mortality tables and applying these longitudinally to simulate future deaths.[1,2] The naïve application of this approach is potentially problematic, as mortality statistics are records of the past, not predictions of the future: they document solely the proportion of people in a population of a specific age and sex in a given year who died in a given year, not how these rates are expected to change in future. As a result, models that apply historical rates in this manner assume general population mortality rates will remain static over time. This is contentious, as general population mortality has improved substantially as societies have advanced. Furthermore, they are predicted to improve further in future, despite the

short-term impact of the COVID-19 pandemic.[3,4] Consequently, application of a static approach to mortality modelling may result in the survival of future populations being underestimated, and associated cost-effectiveness estimates being biased.

Modelling future population mortality is not the exclusive domain of health economists. For example, demographers simulate future death rates in order to predict the future size and composition of societies. This data is then used to inform national planning decisions, including regarding future investment in NHS services.[5] Similarly, actuarial scientists model future mortality in order to estimate the financial risk associated with pensions and life insurance policies. In these fields, future dynamics in mortality rates are commonly modelled.[6,7] Typically, these predictions draw upon historical trends in mortality and changes in mortality associated explanatory variables. For example, the Office for National Statistics (ONS) in the UK produce national population projections every 2 years by age and sex based upon expert panel views informed by target mortality improvement rates and historical trend data.[8] In an academic setting, Janssen et al produce a more disaggregated prediction of future life expectancy for 18 countries in Europe considering the impact of smoking, obesity, and alcohol.[4] Drivers of future life expectancy are complex and include economic growth, investment and policy drivers within health and social care, the speed of development of medical technologies, migration trends and exposure to risk factors such as smoking, obesity and alcohol use.[4,9] Whilst predictions of the future are inherently uncertain, the transparent, evidence-based, and hypothesis driven extrapolation of historical mortality data appears more likely to generate accurate estimates of future mortality rather than simply assuming it is static over time. Despite this, to our knowledge, dynamic modelling of general population mortality has yet to be applied in cost-effectiveness analysis.

In this brief report, we implement both conventional static and new dynamic mortality general population mortality modelling approaches in an illustrative cost-effectiveness model. This example demonstrates the application of a dynamic approach is technically simple and has the potential to meaningfully impact estimates of cost-effectiveness analysis.

Methods

Case study: NICE TA559

In 2019, NICE issued guidance on use of axicabtagene ciloleucel (axi-cel) for the treatment of diffuse large B-cell lymphoma (DLBCL) (TA559).[10] In the Committee's preferred analysis, it was assumed a proportion of patients treated with axi-cel would go on to experience mortality rates comparable to that of the general population. This assumption was implemented via use of general population mortality rates from 2014-2016, adjusted using a standardised mortality ratio (1.09) designed to simulate the potentially higher mortality in this cohort compared to the public as a whole. As the modelling of overall survival using general population mortality data was a key driver of the axi-cel model, we hypothesized incorporation of dynamic mortality modelling may have a meaningful impact on estimates of cost-effectiveness. Subsequently, this was selected as the case-study for this paper.

Replicating TA559 survival modelling

Overall survival curves from TA559 were replicated following the information provided in the appraisal documentation. Expected survival for axi-cel was estimated using a Weibull mixture cure

model as detailed in the manufacturer's submission: constant 0.42, gamma 0.42, cure-fraction 0.5. Survival for the comparator, best supportive care (BSC), was estimated using a Gompertz curve with shape -0.0850 and scale 0.1864, which proved roughly equivalent to the curve provided in the slides for the final NICE committee meeting. Within the response to the first Appraisal Consultation Document the manufacturer submitted a weighted average of two Gompertz curves fitted to patients who did and did not receive a stem-cell transplant within the SCHOLAR-1 trial. 10% of BSC patients are assumed to receive a stem-cell transplant, which equates to the lower-bound of the committee estimate of 10-15%. In accordance with the committee's preferred assumptions, general population mortality transition probabilities were used as a lower bound to mortality for BSC and to represent the mortality of patients 'cured' by axi-cel. As in TA559, ONS national lifetables from 2014-2016 were applied, and it was assumed patients have a mean age of 56 years and that 33/101 patients are female. In line with the methodology used within the NICE appraisal, an assumption was made that 11/119 patients on the axi-cel arm experienced the same outcomes as BSC rather than axi-cel based on the size of the modified intention to treat (mITT) population relative to the ITT population. The mITT population included all patients treated with at least 1.0×10^6 anti-CD19 CAR T-cells/kg. Patients not receiving this dose were assumed in TA559 to experience the same outcomes as patients receiving BSC.

The final fitted curves for axi-cel and best-supportive care were digitised from the Committee slides showing that the predictions from this case-study recreation using data from the ONS 2014-2016 lifetables[11] were similar to those from the original appraisal (see Supplementary Information).

Calculation of expected general population survival

National population projections mortality assumptions were taken from UK ONS projections.[8,12] The published projections provide data up to 2070. Rates of mortality improvement by age and sex are derived based upon:

- Projection of trends in mortality improvements observed from population and deaths data for the period 1961 to 2019
- Adjustment for the impact of increased mortality during the coronavirus pandemic for people aged 30 and over between 2019 and 2022
- National Population Projections Committee agreed target rates of mortality improvement for 2045 based on the above and assumptions around the method and speed of convergence

Life expectancy is projected to increase under the principal of a 1.2% long-term improvement rate up to age 90 for the UK and constituent countries between 2020 and 2045. This trend is continued between 2045 and 2070.

ONS mortality rates were firstly used to calculate expected general population survival assuming an assessment year of 2022 and a weekly model cycle. The age profile from the TA559 case study was used to calculate general population mortality under 4 different assumptions around age distribution: fixed mean age of 56 (based upon a lifetime horizon of 44 years); lognormal, normal, gamma and distributions based on best fit to the available data on the age profile of participants in the ZUMA-1 trial (see supplementary information for further details).

In order to improve comparability of the dynamic and static alternatives, the static TA559 model was updated using 2020 ONS mortality rates (the most recent historic data available). The model assumes that 33/101 patients are female (based on the ZUMA-1 trial) and accounts for the change in male:female balance over-time as different mortality rates are applied by age and sex. In the absence of any trial data on the correlation between age and sex the same age profile was assumed at baseline for both sexes. Scenario analysis was conducted using National Cancer Institute Center for Cancer Research DLBCL age/sex data accessed via cancer.gov.[13] For the dynamic mortality approach the mortality rates used by age and sex were updated per modelled year with the first modelled year using 2022 rates in the current year comparison, the second modelled year using 2023 rates and so on until the time horizon of 44 years was reached. The impact of utilising the alternative mortality projections derived by Janssen et al was tested in scenario analysis.[4,14]

In order to further explore the impact of considering dynamic mortality trends, an additional purely hypothetical scenario was explored. In this analysis, it was assumed axi-cel was launched and evaluated by NICE in 1983. This scenario was designed to illustrate the impact of applying a static approach using mortality data available at the time in comparison to the subsequently observed dynamic reality. Whilst this is not immediately of relevance to forward-looking models developed today, it is nevertheless illustrative of the potential bias associated with failing to account for future mortality trends in economic modelling. The year 1983 was selected for this analysis, as the earliest timepoint for which mortality data is available is 1981, and it was assumed a 2-year turnaround would be required for publication. Subsequently, this was the earliest possible year this scenario could be tested. In this additional analysis, we derived cost-effectiveness results using both a static and an observed dynamic approach and then compared the estimated results. The model time horizon was fixed to 37 years as this was the limit in available observed data.

Accounting for uncertainty around future general population survival

The ONS do not provide estimates of uncertainty around their predictions of future mortality trends. As a result, it was not possible to perform meaningful probabilistic sensitivity analysis (PSA) of this model input. In contrast, Janssen et al. do provide confidence intervals (90 and 95%) for their estimates..[4,14] As a result, it was possible to perform PSA using this data. . This was achieved by first deriving lognormal distributions for each age, year and sex based upon the presented 90 and 95% confidence intervals. Subsequently, random sampling across 1,000 runs was undertaken to explore the impact of this uncertainty on the model outcomes. As there is highly likely to be a correlation in mortality projections across years, a common random number was utilised to sample from each age/sex distribution in a given model run. . Only general population mortality was included within the probabilistic analysis. This is because insufficient data was available within theTA559 submission to enable this to be undertaken.

Presentation of results

The difference in life years between the dynamic and static mortality approaches was estimated undiscounted and using a 3.5% discount rate.[15] This was done separately for a general population cohort with the age profile from the axi-cel case study, and for the incremental life years between axi-cel and BSC. Cost-effectiveness implications were calculated by deriving estimates of the difference in the economically justifiable price of axi-cel for the two approaches. This approach was taken rather than adding costs into the model, as the UK price for axi-cel was marked as commercial in confidence in the TA599 appraisal. Firstly, the difference in quality-adjusted life years (QALYs) between approaches was calculated assuming that the difference in life years

gained between the dynamic and static mortality approaches comes only from the progression-free state in line with the TA559 model. An average utility of 0.76 was applied based on a scenario analysis presented in the NICE appraisal. This value was chosen as the utility values used in the TA559 base case model were redacted. The economically justifiable price (eJP) was then calculated using a willingness to pay threshold of £50,000 per QALY, as axi-cel was deemed to have met NICE's end-of-life criteria in TA559.[10]

Base case results were derived using deterministic analysis..[16] Scenario analysis applying general population mortality rates probabilistically is presented in the Supplementary Information. This includes mean and 95% confidence intervals for predicted life-years, QALYs and eJP.

Results

Including dynamic calculations of mortality increased the undiscounted life years attributed to general population mortality by 2.4 – 3.3 life years (12.7 - 12.8%), across all the weight distribution methods used (Table 1). Whilst the predicted life years increased in both arms within the TA559 case study as would be expected implementing dynamic mortality had a larger impact on the axi-cel arm where are higher proportion of patients were assumed to follow the general population trend. This led to an increase in the undiscounted and discounted incremental life years of 0.826 – 1.183 years (13.4 – 13.6%) and 0.380 – 0.450 years (8.1 – 8.9%) respectively, dependent on the method used to model the age distribution. The commensurate impact on the eJP ranged between £14,456 and £17,097.

In scenario analysis, varying the assumed correlation between sex and age had little impact on the model results (Supplementary Table S3). Use of alternative life table projections provided in Janssen et al (Supplementary Table S4 and S5) had a more meaningful impact. In this scenario, the estimated discounted life-year gain associated with axi-cel increased from 0.380-0.450 years (ONS data) to 0.435-0.620 years (Janssen et al. data).Consequently, the eJP associated with axi-cel increased from £14,456-£17,097 (ONS data) to £16,516-£23,575 (Janssen et al. data). The method chosen to calculate the age distribution was more influential when the Janssen et al mortality rates were used. Probabilistic estimates were similar to the deterministic results. In this analysis, inclusion of uncertainty around mortality projections produced variance in the mean increase in eJP of 2-4% at the 95% confidence interval.

For the scenario analysis using historical data, use of dynamic approach increased estimates of the incremental undiscounted life years by 0.778 – 1.520 years (15.9 – 22.3%). The range presented is dependent on the method used for age distribution. Use of dynamic mortality modelling increased estimates of the economically justifiable price of axi-cel by £14,605 - £25,350. Detailed results for this analysis are provide in the Online Supplementary Appendix.

Discussion

We implemented dynamic mortality modelling in a case-study from a prior NICE appraisal. Future projections in mortality rates were taken from the ONS. Introducing dynamic mortality modelling was computationally simple, and easy to implement. Moving to a dynamic approach produced a sizeable change in the model outcomes. Notably, dynamic mortality modelling increased the estimated undiscounted incremental life-year benefit associated with axi-cel by over 0.8 life years

(over 13%) compared to use of a static approach. The difference between approaches was even more striking using historical observed data within scenario analysis. Use of alternative projections derived by Janssen et al. was tested in scenario analysis. The impact of including dynamic mortality in this case was consistent with the ONS-projection and historical data-based approaches. These results provide evidence that moving to a dynamic approach can have a meaningful impact on cost-effectiveness analyses. Consequently, if the projections of future mortality are accurate, application of a conventional static approach could introduce substantial bias into cost-effectiveness analysis. This is likely to be particularly acute for therapies given for a fixed duration that provide substantial long term survival benefits to young people, where the assumption of static mortality has the potential to substantially understate long term survival benefits due to improvements in general population mortality associated with societal progress.

Given the potential impact of including dynamic mortality modelling on estimates of cost-effectiveness, and the inherent uncertainty associated with predicting future general population mortality, we suggest health technology assessment (HTA) bodies require manufacturers to model both static and a range of dynamic approaches to general population modelling. This approach would enable them to better understand whether their decisions are sensitive to the choice of approach utilised, and subsequently reach a considered conclusion regarding a therapy. We also suggest that HTA bodies that apply QALY-shortfall weighting (e.g., NICE) should consider whether estimates of shortfall should be derived based on static or dynamic projections of mortality. If future changes in mortality are not considered when estimating the number of QALYs experienced by healthy individuals, then estimates of the QALY-shortfall are likely to be biased.

Whilst we have applied this method using UK data, similar projections exist for at least 19 other countries.[4,17,18] These include the USA, Canada, France and Germany. As a result, it would be feasible to incorporate dynamic mortality modelling in economic evaluations focused on a large number of countries.

This analysis is not without its limitations. For example, we were unable to conduct probabilistic analysis using the ONS mortality projections, as the ONS do not provide estimates of probability associated with their estimates. In future work, it would be interesting to explore use of structured expert elicitation to derive estimates of probability associated with the ONS projections. This could then enable meaningful probabilistic analysis to be performed using these estimates. PSA was conducted using the Janssen et al data in scenario analysis with minimal impact on the model results; however, implementation of this approach required assumptions to made about dependence between projections across ages, sexes and years which may or may not hold.

. In addition to these issues, it should be noted we did not have access to patient level data on axi-cel. As a result, our analysis is based on reported mean age and sex-split figures not provided by age and assumed distributions for the trial age profile. This lack of data is potentially important, as our analysis demonstrates use of a simple mean age produces different model outcomes compared to use of an assumed age distribution for the trial population. In order to make mortality projections more accurate, it would have been preferable to have had access to more granular data. In addition, it is important to acknowledge that any projections of future population mortality are inherently uncertain. Whilst this is a clear limitation of use a dynamic approach, this issue applies equally to application of a static approach: assuming mortality rates remain static over time does

not resolve uncertainty, it simply forces a specific scenario that conflicts with the views of government statistical bodies, academic demographers and historical trends in mortality. As a result, we consider use of a dynamic approach to be preferable to a static one.

Equally, this work has its strengths. For example, we applied dynamic mortality forecasts from the ONS: the national statistical institute of the UK.[8,16] These projections reflect the considered, evidence-based, opinions of national experts in mortality rate measurement and projection and are based on all births and deaths in the UK. Subsequently, this appears to be a relatively high-quality data source to inform dynamic projections.

We did not consider the potential inter-temporal dynamics in other model inputs. For example, as society progresses it is likely that morbidity at a given age will reduce, and that subsequently, average quality-of-life for people at a given age will increase over time.[19] We did not capture this potential future dynamic, although it would be interesting to consider this in future work. Within our case study we have also assumed that mortality trends over time will evolve similarly in people with DLBCL who are long-term survivors in comparison to the general population/The validity of this assumption in future models may questionable in diseases such as lung cancer or diabetes which are strongly correlated with risk factors such as smoking or obesity. In these cases, use of the methodology allowing for risk to be accounted for presented by Janssen et al may be more appropriate. Finally, interventions increasing life expectancy may also contribute to the improvements of mortality rates although practically the impact of this is expected to be negligible in most cases.

In conclusion, health economists conventionally apply a static approach to general population mortality modelling that is likely to overstate long-term mortality due to the lack of consideration of social progress. In response, we believe it preferable for health economists to learn from demographers and actuarial scientists and apply a more considered approach to simulating future dynamics in general population mortality rates. In this paper, we have demonstrated this is relatively simple to do, and has the potential to have a substantial impact on estimates of cost-effectiveness. As a result, we call on health economists and HTA bodies to move towards use of dynamic mortality modelling in future.

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Table 1: Model Results

	Age distribution		Fixed	Lognormal	Normal	Gamma
General population mortality	LYs assuming static mortality	Undiscounted LYs	26.279	20.583	18.852	19.411
		Discounted LYs	16.583	13.939	13.060	13.354
	LYs accounting for dynamic mortality	Undiscounted LYs	29.611	23.221	21.251	21.874
		Discounted LYs	17.818	15.060	14.127	14.437
	Difference in predicted LYs	Undiscounted LYs	3.332	2.638	2.399	2.463
		Discounted LYs	1.234	1.122	1.066	1.083
	Difference in predicted LYs (%)	Undiscounted LYs	12.7%	12.8%	12.7%	12.7%
		Discounted LYs	7.4%	8.0%	8.2%	8.1%
Axi-cel: TA559 case study	LYs assuming static mortality	Undiscounted LYs	12.291	9.633	8.834	9.093
		Discounted LYs	7.970	6.716	6.304	6.442
	LYs accounting for dynamic mortality	Undiscounted LYs	13.829	10.823	9.908	10.199
		Discounted LYs	8.549	7.233	6.792	6.940
	Difference in predicted LYs	Undiscounted LYs	1.537	1.190	1.074	1.106
		Discounted LYs	0.579	0.517	0.488	0.497
	Difference in predicted LYs (%)	Undiscounted LYs	12.5%	12.4%	12.2%	12.2%
		Discounted LYs	7.3%	7.7%	7.7%	7.7%
BSC: TA559 case study	LYs assuming static mortality	Undiscounted LYs	3.484	2.896	2.722	2.777
		Discounted LYs	2.388	2.124	2.040	2.068
	LYs accounting for dynamic mortality	Undiscounted LYs	3.839	3.169	2.971	3.032
		Discounted LYs	2.517	2.238	2.148	2.177
	Difference in predicted LYs	Undiscounted LYs	0.355	0.274	0.248	0.255
		Discounted LYs	0.129	0.114	0.108	0.110
	Difference in predicted LYs (%)	Undiscounted LYs	10.2%	9.5%	9.1%	9.2%
		Discounted LYs	5.4%	5.4%	5.3%	5.3%
Incremental: TA559 case study	Difference in incremental life years	Undiscounted LYs	1.183	0.916	0.826	0.851
		Discounted LYs	0.450	0.403	0.380	0.388
	Difference in incremental life years (%)	Undiscounted LYs	13.4%	13.6%	13.5%	13.5%
		Discounted LYs	8.1%	8.8%	8.9%	8.9%
	C/e implications*	Increase in justifiable price	£17,097	£15,304	£14,456	£14,726

Key: BSC, best supportive care; C/e, cost-effectiveness; LYs, life years

* Economically justifiable price calculated assuming that the difference in mortality approaches drives a gain in QALYs within only the progression-free state and a PFS utility of 0.76 based on unredacted scenario analysis value from TA559 and willingness to pay threshold of £50,000 per QALY