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Human Gene Therapy

DOI:
https://doi.org/10.1089/hum.2022.056

Published: 16/09/2022

Peer reviewed version

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Methods for Extrapolating Survival Analyses for the Economic Evaluation of Advanced Therapy Medicinal Products

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Short title:

ATMP Survival Extrapolation Methods

Keywords:

Advanced therapy medicinal products; survival analysis; economic evaluation; cost-effectiveness analysis

Abstract

There are two significant challenges for analysts conducting economic evaluations of advanced therapy medicinal products (ATMPs): (i) estimating long-term treatment effects in the absence of mature clinical data, and (ii) capturing potentially complex hazard functions. This review identifies and critiques a variety of methods that can be used to overcome these challenges. The narrative review is informed by a rapid literature review of methods used for the extrapolation of survival analyses in the economic evaluation of ATMPs. There are several methods that are more suitable than traditional parametric survival modelling approaches for capturing complex hazard functions, including, cure-mixture models and restricted cubic spline models. In the absence of mature clinical data, analysts may augment clinical trial data with data from other sources to aid extrapolation, however, the relative merits of employing methods for including data from different sources is not well understood. Given the high and potentially irrecoverable costs of making incorrect decisions concerning the reimbursement or commissioning of ATMPs, it is important that economic evaluations are correctly specified, and that both parameter and structural uncertainty associated with survival extrapolations are considered. Value of information analyses allow for this uncertainty to be expressed explicitly, and in monetary terms.

1 Introduction

Advanced therapy medicinal products (ATMPs) are a relatively new, and rapidly expanding, category of medicinal products.[1,2] They include, somatic-cell therapy medicines, such as chimeric antigen receptor T-cell (CAR-T) therapies; tissue-engineered medicines; and gene therapies.[3] Medicines that are ATMPs are among the most expensive in the world, with some exceeding £1 million per patient.[4] Evidence on their value is therefore important to justify reimbursement and patent access.

Health technology assessment (HTA) organisations typically assess value based on economic evaluations, which estimate the incremental cost per unit improvement in health outcome – often combining quantity and quality of life. Evaluations require an analytic time horizon that is sufficiently long to capture all plausible differences in costs and effects between an ATMP and comparator treatments (including best supportive care).[5] For ATMPs that are expected to increase survival, a lifetime horizon must be applied to avoid time-horizon bias. Mature clinical evidence could be used to inform a lifetime horizon; however, this is rarely available at the point of marketing authorisation and reimbursement decisions.[4] Instead, survival analyses are necessary to extrapolate estimates of long-term survival from clinical trial data.[6] Such methods underpin the economic models used in the health technology assessment of ATMPs but present analysts with two significant challenges: (i) estimating treatment effects (i.e., survival) beyond the end of the trial and (ii) capturing potentially complex hazard functions.

There are several reasons why a hazard function may be complex. One example of a mechanism that would generate a complex hazard function is a treatment that cures a proportion of patients, resulting in a plateau in long-term survival. Hazard functions may also be complex by virtue of their non-linearity, for example, mortality may be high immediately after treatment but reduce over time. Traditional parametric survival analyses often fail to capture such complex hazard functions adequately.[7,8]

Issues surrounding the extrapolation of survival analyses for cost-effectiveness evaluations are well known.[9–12] These are particularly important in the case of ATMPs where data are often collected in single-arm trials with surrogate end points, leading to uncertainty in long-term treatment effects.[4,13–15] A review of the health economic literature concerning ATMPs highlighted the lack of long-term clinical trial data as a methodological problem for many

studies, often forcing researchers to rely on additional assumptions, resulting in curative claims being made with insufficient evidence.[3] A recent empirical study compared four different economic evaluations of a gene-therapy and found that treatment effect duration was the parameter with the greatest influence on the cost-effectiveness outcome in all four economic evaluations.[15] There is therefore a clear need improve the reliability and precision for extrapolations of survival in ATMPs.

This paper aims to review and critique methods for estimating survival in the absence of mature clinical data in the economic evaluations of ATMPs as well as making recommendations for using these methods for the HTA of ATMPs.

2 Methods

Recognising that an increasing number of ATMPs are under development and will be seeking market authorisation in the near future,[2] we conducted a rapid review[16] using electronic databases (PubMed, Google Scholar), manual searches of recent issues of key journals, and using "pearl-growing" search methods,[17] to identify methods relevant for the extrapolation of survival analyses in the economic evaluation of ATMPs.

Specifically, PubMed, EMBASE, and Google Scholar were searched for articles published to 31st July 2021 using the following terms combined with appropriate Boolean operators: ATMPs, Advanced therapies, cell therapy, gene therapies, expert elicitation, survival modelling and extrapolation. Studies were considered eligible for inclusion if they made reference to the application of methods that would aid analysts in generating plausible estimates of survival and associated uncertainty. The reference lists of included studies were scanned for further relevant articles. Additionally, given the speed of development in this area, we also monitored new publications in the journals Value in Health, PharmacoEconomics and Medical Decision Making up to October 2021.

Three-hundred and seventeen articles were identified via electronic databases, to which 32 articles were added via pearl growing, and a further 8 from more recent scanning of selected, key journals. Of these, 83 were considered eligible for inclusion and deemed relevant to inform the present review.

Identified methods were grouped based on whether they address: (i) extrapolation uncertainty (parameter or structural), (ii) modelling complex hazard functions, or (iii) extrapolation in the absence of mature clinical data. A narrative review of the methods and applications is provided.

3 Addressing Uncertainty

The results of survival analyses and their extrapolations are one source of both *parameter uncertainty* and *structural uncertainty*. Parameter uncertainty is the uncertainty in the values assigned to parameters and is commonly handled using probabilistic sensitivity analysis.[5,18,19] Structural uncertainty arises as decision modelling aims to simplify complex problems, however, as there is often more than one plausible modelling approach, uncertainty is thereby introduced into the decision modelling process.[20–22] Two important

sources of structural uncertainty in the extrapolation of survival analyses are the choice of statistical model and the data used.

A decision based on an analysis of uncertain evidence will also be uncertain, risking the possibility of an incorrect (or sub-optimal) decision. This will have both sunk costs associated with changing clinical practice (e.g., in relation to the provision of ATMPs, staff training, equipment procurement) and opportunity costs in terms of reduced net benefit to population health. Uncertainty in decision models can be characterised using value of information (VOI) techniques.[23,24] It is important, from a policy perspective, that decision uncertainty is explored and reported, as it may be better to delay a decision until uncertainty is reduced through further research.[18,23,24]

3.1 Deterministic/scenario analysis

Deterministic and scenario analyses are used to understand the sensitivity of decision models to specific parameters.[25] Some of the modelling methods (described in section 4) may be particularly sensitive to single parameters. “Even if”/threshold deterministic sensitivity analyses could be used to assess the sensitivity of the decision to such parameters.[24] Deterministic sensitivity and threshold analyses can be well suited in the context of highly uncertain evidence, such as that encountered in the analysis of ATMP trial data. However, they also have limitations, as the range of values chosen is often arbitrary, they do not account for correlation among parameters or for non-linear relationships, and the outputs of deterministic sensitivity analyses may not adequately address the needs of decision makers.[26]

3.2 Structural uncertainty

Different modelling choices can lead to high levels of uncertainty. For example, mean survival estimates for patients treated with a CAR-T therapy in a study comparing non-cure and cure versions of Weibull and generalised gamma models ranged from 2.0 and 3.0 years for each of the non-cure models, to 15.7 and 17.5 years for the cure models.[27] Despite the obvious importance of addressing structural uncertainty, it is often not assessed with the same rigour as parameter uncertainty.[21,24,28,29] Indeed, choosing a single model implies that no others are reasonable and is unlikely to be suitable for capturing the structural

uncertainties associated with survival model extrapolation.[21,30] Model averaging and model parameterisation are two methods for addressing structural uncertainty.

3.2.1 Model averaging

Model averaging is a technique for combining the results of multiple plausible models, and for characterising statistical structural uncertainty. Model averaging takes the average of a set of candidate models and may be weighted by a measure of goodness-of-fit or prior probability.[20,21,30,31] Selecting models for the candidate set to be averaged should not be based solely on goodness-of-fit criteria (e.g., Akaike Information Criterion, AIC) but should also consider plausibility, given that goodness-of-fit to the observed data provides no information about the accuracy of extrapolation.[32–35]

Structural uncertainty is especially important when making long-term extrapolations when equally plausible modelling approaches are possible, and where model averaging provides a more accurate mean effect and a more reliable estimate of precision.[30] The uncertainty estimates from model averaging can then be used in probabilistic sensitivity analyses and VOI analyses.[20,21,30] However, the VOI analysis will only inform the value of reducing the parameter uncertainty and not the structural uncertainty.[21]

3.2.2 Model parameterisation (model expansion)

Structural uncertainty may be considered explicitly by expanding the model to encompass the set of plausible methods identified by the analyst as additional uncertain parameters.[21] Use of generalised distributions is one way of parameterising a model. For example, using the three-parameter generalised gamma distribution instead of distributions that are special cases of the generalised gamma (e.g., Weibull, Gompertz, and lognormal). A second option, which allows models that do not share a generalised form, or are based on different assumptions to be considered in a single model, is adding a parameter to the decision (rather than statistical) model. Bojke and colleagues[20] demonstrate one method of including structural uncertainty in decision models, by introducing an “uncertain parameter” with a beta distribution to the represent the choice between a Weibull and Gompertz distribution. Model parameterisation may be preferable to model averaging, as it is possible to estimate the structural uncertainty separately from the parameter uncertainty and therefore, the VOI can be estimated separately.[20,21]

3.3 Value of information

Value of information refers to a set of methods that can be used to quantify the value of research in reducing decision uncertainty.[36] In this section, two specific VOI methods that are particularly relevant to addressing uncertainty in the extrapolation of survival analyses, are discussed.

The first of these methods is the expected value of perfect information (EVPI), which is the expected cost making the "wrong" decision, or more specifically, the probability of making the wrong decision multiplied by the average cost of making the wrong decision. Consequently, it is the upper bound for the value that additional evidence can provide by reducing uncertainty in a decision problem and is often used as a measure of uncertainty.[18,23–25,37]

The second relevant VOI method is the expected value of perfect parameter information (EVPPI),[18,38] which is similar to EVPI, but rather than expressing uncertainty for the entire decision problem, it is used to express uncertainty in individual parameters or groups of parameters. EVPPI can (and should) be used to understand the sensitivity of the decision problem to the uncertainty of the long-term treatment effects (as well as other parameters). EVPPI can be applied specifically to the uncertainty associated with structural uncertainty when model parameterisation (expansion) has been used to account by calculating the EVPPI for the uncertain parameter described in section 3.2.2.

The nature and maturity of the clinical evidence for many ATMPs means that it is likely there will be significant uncertainty surrounding their long-term effects. In situations where the expected VOI exceeds the expected net benefits of the medicine, HTA organisations might withhold approval and recommend that further research is conducted.[23]

4 Modelling complex hazard functions

There are a variety of survival models that can be used to model complex hazard functions, some of which are already being applied to ATMPs. For example, a systematic review of cost-effectiveness models for CAR-T therapies which use survival analyses to extrapolate long-term survival, identified 20 relevant cost-effectiveness models.[39] Of these, 10 used mixture cure models, three used spline-based models to account for the "curative intent" of CAR-T therapies, three used traditional parametric distributions, and the remaining four

used microsimulation or optimisation to estimate the proportion of patients in each health state. The National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) in the UK has provided an overview of several of these survival model approaches;[32] however, the appropriateness of models for complex hazard functions is not yet fully understood and is a rapidly evolving area of research. Below, we provide an overview of such models and consider their utility for modelling survival in the economic evaluation of ATMPs.

4.1 Mixture models

Mixture models are useful when a single parametric distribution would fail to capture the complexity of the hazard function, but a mixture of distributions would.[40] Mixture models can account for complex hazard functions better than standard parametric models,[41] however, the different hazard distributions for each component should be biologically or actuarially plausible.[8,42,43]

4.2 Cure models

Curative treatments can result in complex hazard functions as survival rates are heterogenous. Kearns et al.[33] for instance, presented a scenario in which cured patients were assumed to have general population mortality, whilst uncured patients were assumed to experience disease-specific death in a relatively short timeframe. Based on their example, Figure 1 shows that the hazard function is complex when the cure proportion is neither 0% nor 100%, meaning it is unlikely that standard parametric models would be suitable.

Cure models have been used for some time and assume that a proportion of the population will never experience the event of interest (e.g., disease-specific mortality).[44,45] Methods that account for the cured proportion can produce more reliable extrapolations than when the cure fraction exists but is not taken into account.[27,32,33,42,46] Accordingly, cure models may be attractive when evaluating ATMPs with curative claims.

Mixture models include mixture cure models and the promotion time cure models.[32,46,47] While both types rely on estimating a cured proportion, they are sensitive to misspecification, and require mature data to accurately estimate the cure proportion.[8,33] Cure models with weak structural assumptions are preferred as they are less sensitive to misspecification.[33]

There are longstanding concerns regarding the use of cure models in survival analysis, in particular the uncertainty surrounding estimates of cure proportions, especially in small samples.[32–34,48,49] These concerns are particularly pertinent in the case of ATMPs. A review of economic evaluations of ATMPs highlighted the dearth of suitable clinical evidence supporting long-term curative assumptions as a major limitation.[3] Therefore, it may only be reasonable to assume that a cured proportion exists once mature clinical evidence has been collected or surrogate measures of survival have been validated. Kearns et al.[33] specifically caution that, "with short follow-up, there is a danger that no model will provide useful predictions of the future."

The Institute for Clinical and Economic Review has recommended that cure models are used as standard in the economic evaluation of "single or short-term transformative therapies" (including ATMPs).[50] However, as this recommendation is based on a single comparison of a cure model with a flexible parametric curve, and a standard parametric survival analysis without cure proportion or flexible parametric curve,[51] it is not possible to attribute the improved performance to the cure proportion, the flexible parametric curve, or even the combination of the two in the model. In a review of flexible models, NICE suggests that cure models could be useful when the assumption of cure is reasonable, but stated that cure models offered few advantages over flexible parametric models that include background mortality in a relative survival or excess mortality framework.[32]

For cure models to be valid in the evaluation of ATMPs, it is important that the assumption of a cure can be supported by evidence and that a reasonable estimate of the cure proportion can be made. This may be based on expert opinion, biological information, data from earlier phase trials with longer follow-up.[33,49] In most instances, regulatory trial data alone are unlikely to provide sufficient information to estimate cure fractions for health technology assessments[49] because the time required to observe a cure is often far greater than the follow-up of clinical trials.[52]

Model choice and the source of data may impact estimates of cure proportions.[53] Therefore, tt is also important to estimate uncertainty in the estimate of the cure proportion, so that appropriate sensitivity and VOI analyses can be undertaken (section 3.3). For example, the sensitivity of results to the assumption of a cure can be assessed by comparing non-cure mixture models to the equivalent cure mixture model. This could be a deterministic

sensitivity analysis, or model parameterisation to estimate the structural uncertainty resulting from the assumption of a cure. This may appear to be statistical minutiae, however even when cure and non-cure mixture models estimate similar cure/low-mortality proportions, there may be substantive differences in mean survival estimates.[8] Consequently, it would be reasonable to expect substantive differences in estimates of health outcomes.

4.3 Generalised linear model framework

A variety of models in the generalised linear model (GLM) framework can be used to model survival.[35] Restricted cubic spline models, a type of piecewise polynomial, are one extension of the GLM and have been recommended as appropriate for modelling complex hazard functions.[54] It has been suggested that piecewise models are more efficient than mixture models for complex hazard functions that result from a cure proportion.[32]

In the context of survival analysis, restricted cubic spline functions split time at a given number of knots (*k*), where the first and second derivatives of the function must agree at each of the knots and the tails are constrained to be linear.[54–57] Such models are able to describe complex functions, with five knots providing sufficient flexibility in most cases[58] – though analysts should aim to keep the number of knots small.[59] Figure 2 shows three different specifications of a restricted cubic spline model (*k* = 3-5) fitted to the 50% cure hazard function from Figure 1.

The linear constraints imposed on the tails of these functions mean that extrapolation will be linear (on the scale modelled), which may not be actuarially plausible and therefore, should not be naïvely accepted. Using external data would be one way to inform this decision. In one comparison of traditional parametric methods (Weibull, exponential, Gompertz, log-logistic, log-normal) and restricted cubic spline models for modelling progression free survival in immuno-oncology, the restricted cubic spline models provided a better fit to Kaplan-Meier curves, particularly when the survival function reached a plateau, and provided more realistic extrapolations.[7] Further, it has been suggested that spline based models may produce more credible estimates, by being closer to what is biologically plausible and aligned with expert opinion, than standard parametric models.[60]

A recent case study[35] applied the following raft of models to data from a breast cancer study: fractional polynomials, spline models, generalised linear mixed models, general additive models, and dynamic GLMs (known as dynamic survival models when applied to survival data). The authors suggest that if concerned with extrapolations, dynamic survival models should be preferred on a theoretical basis as parameter estimation is based on minimising forecasting error. The results of the case study did not suggest that any of the GLMs improved extrapolation accuracy, however, the extrapolation of the fractional polynomials, general additive models, and dynamic survival model were plausible given external evidence, whilst none of the extrapolations of the traditional parametric models were considered valid.

4.4 Landmark models

Landmark models assess patients' response to treatment at a *landmark* time point and assign them to separate groups based on this before estimating separate survival models for each group.[61–63] Any of the other approaches discussed may be used, separately, for each of the groups in the landmark model. For example, those who respond to a treatment may have a decreasing hazard of disease-specific mortality, modelled using a mixture cure model; whereas those who do not respond to the treatment may have an increasing hazard, modelled with a restricted cubic spline model.

A major limitation of the landmark method is that it omits events that occur before the landmark time[62] and given that some clinical trials of ATMPs are based on small samples,[13,64] this may result in an unacceptable loss of power and data. In addition, the landmark method assumes that response to treatment is a surrogate for long-term survival and this may not be reasonable given available evidence. Finally, if a landmark model is used, the choice of landmark will influence the results, therefore it is important that this is adequately justified and sensitivity analyses conducted to consider multiple landmark times.[63]

4.5 Poly-hazard models

Poly-hazard models assume that there is an overall hazard function comprised of several additive hazards (e.g., a collection of cause-specific competing risks).[65–67] Each component may have a different distribution; therefore, the overall hazard function has greater flexibility than a single traditional parametric model. An example of a complex overall

hazard modelled using this method would be modelling population mortality as a background risk with an additive hazard function for the mortality risk for the given treatment.[32]

4.6 Relative survival models

Relative survival (or excess hazard) models are a special case of poly-hazard models, comprising the disease specific mortality and the background mortality. Disease specific mortality is usually estimated as the difference between the mortality of the population of interest and a *matched* background mortality, often based on life table data.[68] Disease-specific mortality may also be estimated directly from clinical trial data.[32]

There are several spline-based relative survival models, that may be useful for extrapolating survival in the economic evaluation of ATMPs, imposing different constraints beyond the final knot, reflecting different assumptions about the excess hazard.[69–71] An advantage of relative survival models is that extrapolations will inherently incorporate external data (as the source of background mortality), thereby reducing the likelihood of producing implausible extrapolations. However, it is essential that data for a relevant population is available, to provide an appropriate background mortality rate, which may be more challenging in a clinical trial setting than in the population studies where relative survival models have typically been used.[32]

4.7 Summary

The modelling approaches described above provide analysts with several methods for capturing a complex hazard function when traditional parametric models would fail. However, this does not solve all the issues concerning extrapolation; in the absence of mature clinical data, analysts must decide which model(s) they believe are plausible and, therefore, will use to inform the economic evaluation. This choice introduces significant uncertainty and potential bias into the decision.

It should be noted that following a simulation study to investigate the performance of the extrapolations of eight parametric models, Gallacher et al.[34] concluded that typical trial follow up is rarely sufficient for extrapolations and that “the accuracy and reliability of extrapolations will only deteriorate as data come from more complex underlying hazard

behaviours, especially when the behaviour of the hazard rate is expected to differ beyond the observed period."

5 Extrapolation in the absence of mature clinical data

An empirical model that fits the observed data well will not necessarily provide accurate, or even plausible extrapolations and it is widely recommended that external information (e.g., relevant long-term survival data, expert opinion) is used to inform extrapolations.[6,19,34,41,49] This is highlighted in a recent validation-based case study, which found that flexible models that captured the complex hazard function and incorporated external information extrapolated well, whilst models that did not incorporate external information extrapolated poorly.[43]

There are various sources of external data and associated considerations to be made when using them. Usually, more is known about the natural history of diseases, the efficacy of existing treatments, and the current standard of care, than the efficacy of the new treatment. Below, we discuss three types of data and some important considerations when using them to inform modelled extrapolations of survival analyses to estimate long-term treatment effect: (i) expert opinion, (ii) existing quantitative data, and (iii) clinical trial simulation or model-based meta-analysis.

5.1 Expert opinion

Formally elicited expert opinion has been used widely to estimate parameters in economic evaluations where data (especially in relation to healthcare resource use) are unsuitable or unavailable.[73–81] There have been numerous calls to include expert opinion in extrapolation of survival analyses.[6,82] Indeed, including expert opinion may help to provide more realistic estimates of uncertainty.[83,84] However, reviews of applied studies using expert elicitation have found heterogeneity in the methodology used and a lack of consideration for any existing guidance on the topic.[74,76,85–87]

There are several methods for eliciting expert opinion.[88–91] Whilst these are generic methods for elicitation, rather than being specific for eliciting information to be used in the extrapolation of survival analyses, they may, nonetheless, prove useful when trying to improve the accuracy of extrapolations and can be included with varying degrees of formality. Examples include but are not limited to: the Delphi method,[92] The Sheffield

elicitation framework (SHELF),[93] the "bins and chips" graphical method,[94] probability boxes,[95] and the Expert Elicitation Tool (EXPLICIT).[96] The Delphi method is designed to elicit a consensus, which in the context of economic evaluations, is less useful than the other methods listed, which aim to provide the analyst with both a point estimate of a parameter as well as a distribution.[89] The distribution reflects experts' (un)certainty in the point estimate and is consistent with the Bayesian framework in establishing prior probability distributions.

Given the lack of consistency in the application of elicitation methods, a reference case has been developed to aid analysts and decision makers using expert elicitation in health care decision making.[89,97] The reference case is flexible and provides methods for transparently eliciting a single quantitative distribution for decision problem parameters that reflect the individual beliefs of several experts, the uncertainty of these beliefs, and recommends investigating the reasons for the uncertainty.

Another way of using expert opinion, is to present different extrapolations (scenarios) to clinical experts for feedback on their plausibility. Whilst ideally one would want to elicit expert beliefs *a priori*, it has been suggested that it is more common for clinicians to be consulted *post hoc* to select the most plausible model from a candidate set that is presented to them.[82] This may be a result of constraints on the project (e.g., time).

5.2 Existing quantitative data

Jackson et al.[6] reviewed methods for extrapolating survival from randomised trials using external data (e.g., registries, cohort studies, previous trials, expert opinion) and developed a framework for model choices. Their review highlights several considerations that must be made when using existing quantitative data. Further, they discuss various modelling options for survival extrapolation under the assumption of *systematic differences* between the trial data and external data (e.g., proportional or additive hazards) and methods for adjusting the external data to represent the population of interest.

The framework[6] assumes three populations: a control group, a treatment group, and an external population. If the control (or treatment) population are assumed to have the same hazard as the external population for a given portion of time (e.g., in the short-term, in the long-term, or both) then the control (or treatment) population can be estimated directly

from the external population for that portion of time. Where the hazard is assumed to be systematically different in both the short- and long-term, then the external population must be adjusted to represent the control (or treatment) population.

Firstly, it is important to consider how the external data relates to the study population. Disease registry data may allow the control arm to be extrapolated with few adjustments (e.g., age, sex). Whereas, general population data may be adjusted using proportional/additive hazard models based on understanding of natural history.[6] Secondly, is the consideration of the expected treatment effect. One potential treatment effect of ATMPs would be an initially higher hazard than the general population (it is unlikely to be lower) and at a given point in time, the hazard may be expected to converge with that of the general population (as in Figure 1). After the convergence point, survival of the cured proportion can be estimated from external (matched) population. Alternatively, if the treatment effect is expected to persist and non-time varying proportional/additive hazards can be assumed, then survival for the treatment arm can be estimated from the external data by applying an appropriate proportional/additive hazards model. For example, elicited expert opinion may suggest that there is a long-term hazard ratio (β) for those treated by the ATMP when compared with the control group, therefore, the hazard for the treatment group could be estimated as

$$h_{treatment}(t) = \beta h_{control}(t)$$

NICE recommends that alternate extrapolation scenarios are considered and provide an example of three scenarios to be considered:[19] (i) the treatment effect is nil, (ii) the treatment effect (γ) remains the same, and (iii) the treatment effect reduces in the long-term. Table 2 provides example functions for estimating the hazard for the treatment group from the control group for each of the three scenarios provided by NICE.

Hwang and Wang[98] proposed a method that can be used to extrapolate survival beyond the end of follow up (T_f) using a combination of clinical trial data that includes both survival data and relevant covariate data (e.g., age, sex, socioeconomic status) for a treatment population with life table data or any other source of hazard data. This method relies on the following assumptions: (i) the ratio of survival is relatively stable after an initial period of stabilisation (T_s), (ii) the hazard for the treatment population is worse than for the reference population, and (iii) $T_f > T_s$.

If these assumptions are reasonable, then three steps can be used to estimate survival for the treatment population beyond T_f. Firstly, using the as much of the covariate data as practicable, a matched reference population can be simulated from life tables using Monte Carlo methods. Secondly, after applying a logit transformation to the ratio for survival between the treatment and simulated reference population, a linear regression model can be fitted for $T > T_s$. Finally, this regression model can be used to predict survival for the treatment population for $T > T_f$. This method has validated with both simulation and real data and also extended using a rolling extrapolation algorithm to remove the assumption of constant hazard.[99]

5.3 Expert opinion or data from other relevant trials (e.g., of comparable treatments with longer follow-ups) may be used to evaluate the appropriateness of assumptions of systematic differences. Guyot et al. present a method for formally including elicited beliefs and registry data in extrapolations of survival along, with an example.[100]

Pharmacometric model-based analyses

The effect of a drug on disease progression is routinely investigated in drug development using mechanism-based modelling (pharmacometrics), that considers the relationship between drug exposure (pharmacokinetics), response (pharmacodynamics), and the associated uncertainties.[101] Pharmacometric models can then be used to simulate clinical trial results, accounting for subject-specific covariates, imperfect adherence, and different doses.[102] A recent review highlights some of the opportunities and challenges of applying pharmacometric models to the development of gene-therapies (a type of ATMP).[103]

Pharmacometric model-based clinical trial simulation can be used to generate distributions of treatment effects for a range of populations and trial designs[104] which could be incorporated as a source of external data for the extrapolation of a survival analysis. Alternatively, the pharmacometric model could be applied to an ATMP trial population to estimate plausible treatment effects for that specific trial, with a longer follow-up than the actual trial to allow the estimation of long-term treatment effects. Several studies have combined pharmacometric modelling with economic models.[104–107]

Model-based meta-analyses[108] combine pharmacometrics with traditional meta-analytic techniques to generate mechanism-informed projections of the relative effects of treatments. One of the key advantages is that model-based meta-analyses can be used to

synthesise indirect comparisons based on quantitatively established relationships between biomarkers to long-term outcomes, including survival.[109–111] These can serve as priors to quantify how a drug with limited evidence compares to the current standard of care.

5.4 Bayesian methods

Bayesian methods allow researchers to formally incorporate prior knowledge or expectations in their analyses using prior probability distributions, allowing a corpus of evidence to be updated with new information.[112] Information from various sources can be used to build prior distributions (e.g., previous trials, expert opinion, external data, pharmacometric modelling).[104,113] Priors such as these are often described as *informative priors*, as they inform the posterior distribution. However, in a review of clinical trials that used Bayesian survival analyses, Brard et al.[114] found that few trials employed Bayesian survival analyses, and none of the articles reviewed reported using informative priors on the parameters of interest; although more recently a study showed that using previous trial data to inform the prior distribution for the hazard function could improve the extrapolation performance.[113]

Guyot et al.[100] used Bayesian multiple parameter evidence synthesis to combine data from: a randomised control trial, information about general population survival, conditional survival from a cancer registry, and expert opinion in a restricted cubic spline model. The authors of the study concluded that their model outperformed various standard parametric models, some of which produced extrapolations which were deemed implausible. The authors also noted that in data sparse situations, incremental model building was sometimes faced with technical difficulties, however these were overcome when including external data.

The NICE DSU discuss some uses of Bayesian survival analysis, but also notes that its use thus far has been limited and there is potential for it to be used further and for additional research into these methods to be conducted.[32]

6 Concluding remarks and future directions

There is often very little mature survival data for ATMPs; to avoid time horizon bias in economic evaluations, analysts must make extrapolations of trial data, to capture any long-term differences between treatment and comparator in costs and consequences. In the

absence of mature survival data, there are a several sources of information that analysts may use to guide their extrapolations (e.g., existing quantitative data, expert opinion, pharmacometric modelling).

Claims of ATMPs having curative effects must be supported by sufficient evidence if a cure model is to be used; it is also important that the chosen modelling approach is suitable for capturing a complex hazard function. Mixture models (including mixture cure models) and restricted cubic spline models are likely to be more suitable for modelling complex hazard function than conventional parametric approaches. Alternative methods include landmark and poly-hazard models.

For all extrapolations used in economic evaluations, both the structural and parameter uncertainty should be considered formally using probabilistic sensitivity analysis. The results of VOI analyses can help decision makers understand the potential costs of a decision (given current evidence) and the opportunity to reduce this cost through further research.

While there are several options for improving extrapolations in the absence of mature clinical data, the relative costs and benefits of each method are not well understood. It would be prudent, therefore, for future research to compare the performance of each option before recommending any one method above others. Bayesian multi-parameter evidence synthesis, however, provides a formal method for combing evidence from a range of sources and estimating the associated uncertainty.

Authorship Confirmation Statement

DH designed the study, WH reviewed the literature and drafted the article, DH reviewed the article and rewrote large sections.

Authors' Disclosure

No competing financial interests exist.

Funding Statement

The work for this article was funded by the Welsh Blood Service WBS-ITT-46342.

Code Availability Statement

Code used to produce Figures 1 and 2 is available online at https://github.com/w-hardy/atmp-survival-review

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Tables

Table 1. Overview of methods for modelling complex hazard functions and considerations for applying them to ATMPs

Model type	Features	Advantages	Disadvantages
Cure	- Assumes that a proportion of patients will be cured and have the same mortality as a reference population	- Performs better than non-cure models when a cure proportion exists	- It may be difficult to test the assumption of a cure in the absence of mature clinical evidence - When there are few patients at risk in the tail, the estimate of the cure fraction will be highly uncertain
Generalised linear models	- Models hazard functions with GLMs and extensions of them	- Can describe arbitrarily complex hazard functions	- Tails are (usually) restricted to being linear and, therefore, may produce unrealistic extrapolations
Mixture model	- Overall hazard is modelled by a mixture of distributions	- Can model subpopulations (which may or may not be observable) - Can model complex overall hazard functions	- User must specify the number of mixtures and a distribution for each mixture - GLMs may be a more efficient way of modelling complex hazard functions
Poly-hazard model	- Overall hazard is modelled by several additive hazards	- Can model complex hazard functions	- Requires the analyst to specify distributions for each hazard, if there are several plausible options

			for each, this may lead to increased structural uncertainty and complexity in the analysis
Landmark model	- Models hazard for those who respond to a treatment by a given point in time separately to those who have not responded	- Allows the hazard of the responders and non-responders to have different hazard functions	- Assumes all responders will have responded by a given time point - Assumes that response is a surrogate for survival - Sensitive to the choice of landmark time - Reduced power as events that occur prior to the landmark time are not included in the analysis

3

4

Table 2. Example functions for modelling the treatment group hazard function from the control group hazard function under alternate extrapolation scenarios recommended by NICE.

Scenario	Systematic difference	Example functions for modelling treatment hazard function
Treatment effect is nil	None	$h_{treatment}(t) = h_{control}(t)$
Treatment effect remains the same	Additive hazard (AH)	$h_{treatment}(t) = h_{control}(t) + \gamma$
	Proportional hazard (PH)	$h_{treatment}(t) = \beta h_{control}(t)$
Treatment effect reduces in the long term	AH asymptotic reduction	$h_{treatment}(t) = h_{control}(t) + \gamma^{\theta(t)}$
	AH constant reduction	$h_{treatment}(t) = h_{control}(t) + \xi\gamma \; for \; all \; t < t_x$ $h_{treatment}(t) = h_{control}(t) \; for \; all \; t \geq t_x$
	PH asymptotic reduction	$h_{treatment}(t) = \beta^{\theta(t)} h_{control}(t)$
	PH constant reduction	$h_{treatment}(t) = \xi\beta h_{control}(t) \; for \; all \; t < t_x$ $h_{treatment}(t) = h_{control}(t) \; for \; all \; t \geq t_x$

Notes:

$\theta < 0$, ξ = rate of constant decrease, t_x = time where treatment effect is expected to stop reducing or equal 0.

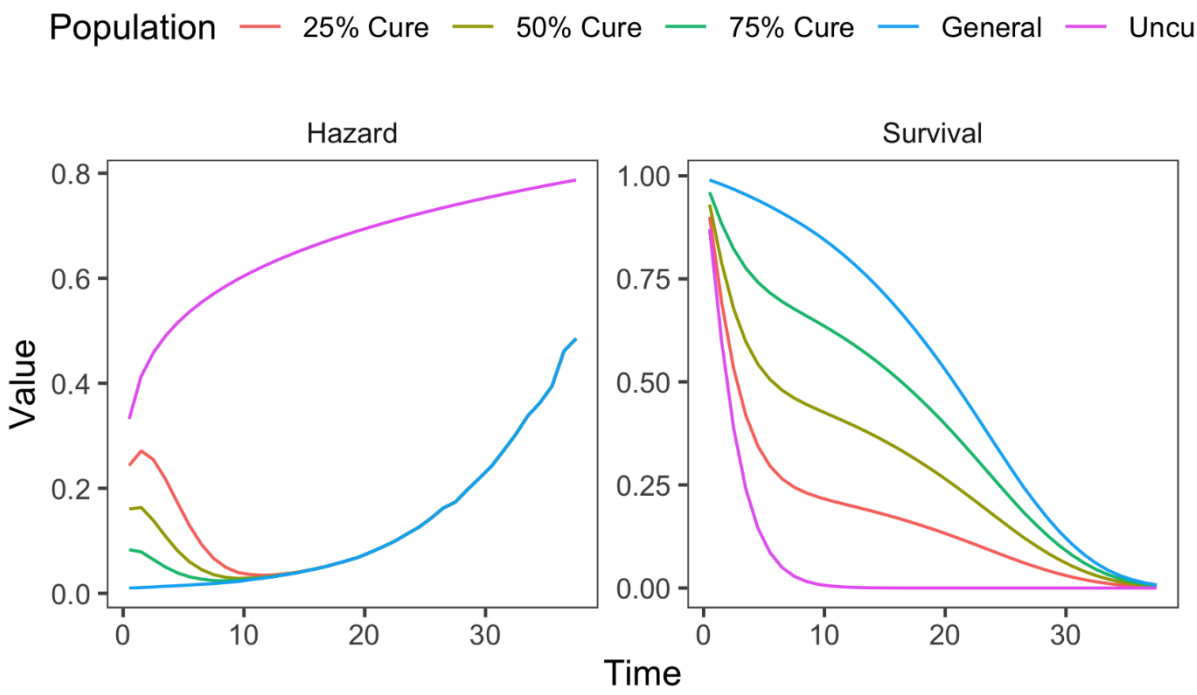

Figure 1. Hazard and survival rates for hypothetical cure scenarios. Adapted with permission from Kearns et al. 2021.[33]

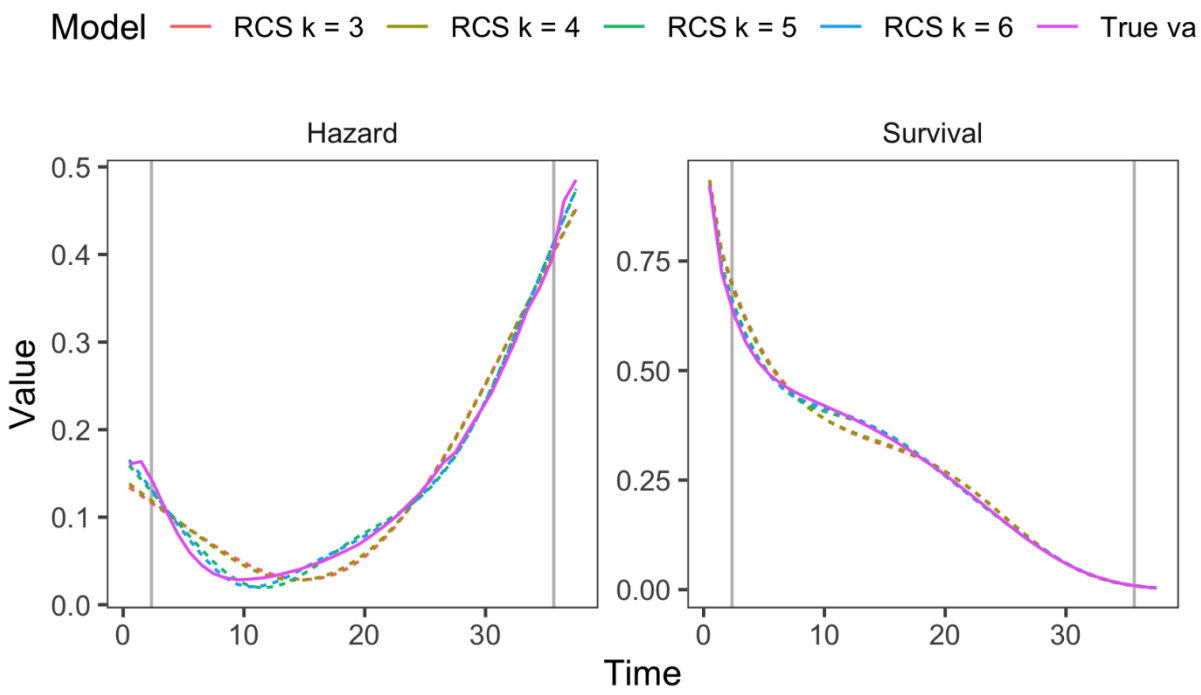

Figure 2. Restricted cubic spline (RCS) models with 3-6 knots (k) fitted to the hazard function of the 25% cure scenario from Figure 1. Grey vertical lines represent the 5th and 95th percentile of time, where the outermost knots are places in the RCS and beyond which the function is linear on the hazard scale.