Employing Bayesian survival and cost-effectiveness modelling for more informed healthcare decision-making: Practical overview and current perspectives

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Executive Summary

Bayesian statistics offers a rigorous approach to integrate historical study or real-world data into survival, cost-effectiveness, and related models that are commonly used in health technology assessments. In this article, we motivate the adoption of Bayesian methods to perform these analyses and explain how Bayesian methods can empower evidence generation for challenging datasets. Then, we discuss current factors hindering more widespread application of Bayesian methods to clinical study data and outline opportunities to employ Bayesian approaches and thereby overcome issues with conventional methods that frequently arise in regulatory and reimbursement submissions.

Key takeaways

- Bayesian models can improve the accuracy, precision, and transparency of treatment efficacy estimates in challenging decision-making scenarios, such as at initial reimbursement when data are immature and in rare diseases or subgroup analyses where sample size is limited.
- The use of Bayesian methods in health technology assessments is likely to continue to increase in the future as payers place further emphasis on early access agreements and precision medicine.

Bayesian methods can empower evidence generation and facilitate constructive engagement of stakeholders

Survival models fitted to time-to-event data from clinical studies, and cost-effectiveness models that extend survival models to multiple health states and incorporate disease-related costs, are common in health technology assessments (HTAs). Health authorities are increasingly encouraging or requiring that estimates obtained from these models are supported by relevant external information sources such as historical study or real-world data.[1] This advancement is greatly facilitated by the recent growth in availability of such data and is becoming more important to the reimbursement process as payers continue to frequently accept less mature study data in HTAs.[2] However, regulatory technical guidance on preferred approaches to incorporate external information into survival, cost-effectiveness, or related models is sparse, and manufacturers often only use external data for basic post-hoc model validation or else integrate prior information into model predictions in a simplistic manner. Crude approaches to incorporate external data into survival models may in fact worsen the accuracy of estimates owing to the introduction of artefacts and ignorance of confounding variables, and therefore may do little to improve payer confidence in predictions of treatment efficacy.

Hence, it is desirable to pursue rigorous approaches to directly and holistically integrate external data into survival and cost-effectiveness models when data are limited by follow-up duration or sample size. A natural solution to this problem is provided by Bayesian statistics,[3,4] which describes a formal framework to synthesize current and external information sources via incorporation of *a priori* expectation, which is often expressed via a prior probability distribution. The prior distribution is specified by the modeler and describes the expected model behavior in the absence of the current study data, as well as the *a priori* uncertainty associated with the external knowledge.[5] These prior data are then combined with the current study data to yield posterior probability distributions for model estimates *(Figure 1)*. Prior distributions impose transparent clinical assumptions pertaining to the choice of external data and the model formulation, and therefore Bayesian models are explainable and may help to constructively engage stakeholders during regulatory and reimbursement processes. Despite their intuitive attractiveness, the adoption of Bayesian methods in healthcare research is currently hindered by issues of complexity in model design and implementation that require specialist knowledge. In the following, we discuss the potential for Bayesian models to improve the rigor of survival and cost-effectiveness analyses in HTAs, and outline opportunities for employing a Bayesian framework to yield robust and precise clinical insights from study data.

Bayesian methods allow selected model features to be informed by relevant external data

The Bayesian framework is not based on the classical notion that the current study data are the sole information source, and therefore better reflects the decision-making scenario in most modern HTAs, where relevant historical trial or observational data in a similar setting are usually available. Instead, Bayesian approaches allow the holistic integration of external knowledge to supplement features of model predictions where observations are scarce, and thus allow proper quantification of uncertainty inclusive of existing relevant data sources, while avoiding overfitting to non-ideal external information.[6,7] Moreover, Bayesian models that are constructed appropriately can tolerate moderate confounding between external and current data sources, which arises from inevitable differences in baseline characteristics of the patient population and in study design, as well as from evolution of the treatment landscape over time. That is, the external data play a limited role in a Bayesian model as a representation of the best available source of *a priori* information on specific model features and the associated prior uncertainty, including uncertainty reflecting a believed lack of commensurability between external and current data sources. In effect, a well-designed Bayesian model can adaptively borrow only from certain features of the external data that are not inconsistent with the current study data, for example, for covariate coefficients associated with selected baseline characteristics, or outside of the current study follow-up period.

Indeed, there are many common scenarios where there is a necessity to leverage non-ideal external data, so that the sophisticated synthesis of disparate information sources offered by Bayesian methods is especially advantageous. An important special case of this situation is when historical study data are only available for the standard of care. While Bayesian modelling strategies may focus on reducing uncertainty in the control arm in this scenario, there is also the possibility that the external control data can be leveraged to construct demonstrably conservative survival models for experimental arms, via implicit treatment waning assumptions. A recent case study analyzed reconstructed data from an interim analysis of a randomized phase III trial of the PD-1 immune checkpoint inhibitor pembrolizumab plus standard of care in first-line advanced cervical cancer, employing a Bayesian model informed by historical trial data with extended follow-up for the control treatment.[8] The Bayesian model correctly forecasted the statistically significant positive treatment effect on survival that was later observed in the final analysis, whereas extrapolations from the uninformed model had high uncertainty *(Figure 2)*. Although, predictions from the Bayesian model were conservative since the implicit treatment waning assumption did not capture the true extent of durable treatment benefit in the experimental arm. Nonetheless, carefully designed models such as these may provide more convincing evidence of treatment efficacy to payers during initial reimbursement submissions, since they avoid naïve speculation and are instead grounded in justifiable assumptions.

In general, prior distributions should be rationalized in terms of the implicit clinical assumptions they entail and their perceived level of conservativeness. When leveraging external data for a therapy in the same or related

class to inform estimates for an experimental treatment, modelers should consider what features of outcomes are anticipated to be shared between treatments, per their mechanism of action. For instance, for novel oncology therapies such as immunotherapies and targeted therapies, the potential for phenomena including delayed responses, durable or transient responses, and acquired resistance should be critically evaluated. Unknown confounding between current and external data sources can be accounted for by increasing the variances of prior distributions to effectively discount the external data, while known differences in the distribution of key baseline characteristics can be accommodated by matching-adjustment if necessary.[9]

Bayesian models facilitate more reliable and justifiable extrapolation of survival outcomes from immature data

Extrapolation of survival outcomes from data with limited follow-up, as in the aforementioned advanced cervical cancer case study *(Figure 2)*,[8] is a ubiquitous task in HTAs and is typically one of the key drivers of cost-effectiveness.[10] Hence, formulation and selection of an appropriate survival model is often a critical consideration influencing payer recommendations, especially when study data are immature. Following the current conventional system to decide upon a survival model,[11] which considers goodness-of-fit to the available trial data as a primary criterion for ranking candidate models and then typically performs naïve extrapolation, risks severely misrepresenting the value of novel therapies when trial data are immature, by failing to capture complex survival patterns borne by longer-term effects.[10] Standard survival models are also liable to misrepresent the true decision uncertainty, owing to the simplistic assumptions surrounding the extrapolation and failure to acknowledge other relevant sources of information outside of the current study. Moreover, when statistical assumptions pertaining to the extrapolation are inadequately justified by external data, the survival or cost-effectiveness model is not readily defensible, and the plausibility of model estimates may not be verifiable. Payers may respond to the consequent high decision risk by expressing a preference for a more conservative model or requiring additional evidence to demonstrate that acceptability thresholds are met convincingly.

A recent application of Bayesian survival models to a phase III trial in metastatic non-small cell lung cancer demonstrated that leveraging historical trial data with extended follow-up for dual immunotherapy enabled the durable survival benefit associated with dual immunotherapy plus chemotherapy to be more accurately captured, compared to traditional models, when study data were immature.[12] That is, the Bayesian model was not naïve to the durable responses in the experimental arm that were sustained beyond the available follow-up period, which are characteristic of immunotherapies, whereas the conventional model underestimated the value of the combination regimen vs chemotherapy by failing to adequately capture this effect. Similarly, informed Bayesian models may accurately forecast deleterious effects that indicate a trial can be prematurely discontinued for reasons of patient safety and to avoid wasting resources.[13] These qualities of Bayesian models

to perform informed trial-based survival extrapolations are also beneficial for indirect treatment comparisons, where leveraging long-term external information can mitigate bias arising from differences in follow-up duration across studies.[14]

Bayesian models can enhance predictive power to enable precision medicine

Subgroup analyses are usually exploratory by study design but are often critical to ensure payers can assess where novel therapies yield the most value and thus identify a policy for optimal allocation of resources. High uncertainty in subgroup-specific estimates often precludes quantitative understanding of treatment benefit among specialized patient populations and stakeholders may be unwilling to accept evidence of treatment effect within clinically important subgroups because of apparent statistical insignificance. In a Bayesian formulation, subgroup-specific historical study data can be leveraged to reduce uncertainty in estimates derived from the current study, and thus aid manufacturers in demonstrating efficacy when sample sizes are small. In a recent application, data from a phase I study of immunotherapy in a gynecologic cancer, stratified 1:1 according to a key tumor biomarker, were leveraged to aid an exploratory analysis for the subgroup exhibiting the favorable but less common biomarker in the phase III trial data, which was underpowered since enrolment in the phase III study reflected natural prevalence of the biomarker (around 1:3 ratio).[15] This strategy has wider applicability to yield detailed clinical insights on the efficacy of novel oncology therapies, as it is becoming increasingly common for earlier-phase non-randomized studies to perform selected enrollment of patients exhibiting a clinical biomarker that is amenable to the treatment mechanism of action, while randomized phase III studies follow an all-comers design.[16]

In general, it may be difficult to source subgroup-specific external data owing to limited capture of information on key baseline biomarkers, especially in real-world data sources. In this situation, it has been suggested that subgroup analyses can be aided by "borrowing" information from the complementary subgroup within a Bayesian framework.[17] Bayesian methods are now routinely adopted for augmentation of control arm populations in rare disease studies,[18] where sample size challenges likewise preclude precise quantitative inference on treatment effects, and therefore their potential application to enhance predictive power in subgroup analyses is already clear. As payers place increased emphasis on optimizing outcomes for more granular patient populations,[19] a task to which traditional statistical methods employed in HTAs are not well suited, the appeal of alternative Bayesian approaches to perform subgroup analyses and thereby facilitate precision medicine will continue to grow.

Outstanding challenges remain for the adoption of Bayesian methods in HTAs

Despite the advantages of adopting a Bayesian framework to survival and cost-effectiveness analyses, there is a requirement for specialist expertise that is arguably a main hindrance to more widespread use of these methods. While the potential to sophisticatedly integrate external data into models is powerful and appealing, the resulting complexity creates additional responsibility for modelers to carefully design and justify the precise model formulation.[20] Specifically, modelers must consider factors such as the choices of external data, the mechanism for its inclusion, and validation of model estimates through conducting scenario analyses. A qualified modeler will be fluent in the underlying mathematics of Bayesian statistics[21] and practical aspects of model estimation by Monte Carlo methods,[20] familiar with a probabilistic programming language such as Stan,[22] and experienced in applying Bayesian models to clinical data.

While some influential health authorities have provided arguments in favor of Bayesian methods,[23] there is currently a lack of specific technical guidance from regulators or payers on precise aspects of Bayesian model design and validation. The FDA recognizes the usefulness of Bayesian methods for improving the precision of treatment effect estimates, especially in subgroups and rare diseases, but the current FDA guidance is primarily focused on the perspective of clinical trial design rather than evidence generation.[24] The FDA emphasizes early engagement to align on implicit model assumptions related to the choice of priors.[25] Guidance from the National Institute for Health and Care Excellence (NICE) advocates for Bayesian methods as an approach to incorporate pre-defined understanding of specific risks on survival and mentions several particular classes of Bayesian model that can be considered for informed survival extrapolations, but does not offer detailed technical advice on preferred modeling practices.[26] Currently, detailed guidance on best practices for informed Bayesian survival and cost-effectiveness analysis is primarily contained in the academic literature.[6, 27-29] In the future, the prevalence of Bayesian models in HTAs will likely increase owing to the improved availability of specialist software[30] and a greater number of case studies demonstrating the practical benefits of, and providing direction on best practices for, Bayesian methods across a diverse array of decision-making scenarios and therapeutic areas.

Following best practices provides many opportunities for Bayesian methods to improve evidence generation

For successful implementation of Bayesian methods to generate evidence for payers, regulators, and clinicians, manufacturers should survey and collect relevant external sources of patient-level data – observational data, data from earlier-phase trials, and data from previous randomized studies of related patient populations and therapies - that provide high-quality *a priori* information to supplement observations from an ongoing study. In typical applications, there is little advantage to incorporating many distinct sources of external data, and instead

it is usually most appropriate to select the single most appropriate external dataset to derive prior expectation, and if appropriate, explore other external data sources in scenario analyses. Higher-level information such as population-level quantities or clinical expert opinion may also be gathered to serve as prior knowledge.

These data can then be used to inform a Bayesian model that is designed appropriately to gain predictive power from the external data, considering the aspects of the current study that would benefit most from being supplemented, while recognizing the limitations of the prior information sources. For example, if sample size is satisfactory but data are immature, a survival model can be formulated with sufficient flexibility that longer-term external data essentially only affect estimates beyond the follow-up period.[3] If a study was underpowered to assess some subgroups but not others, then informed prior distributions may be employed only for selected covariate coefficients. During the model design process, input from clinical experts and other stakeholders should be sought to validate the assumptions that are implicitly invoked by the model design, and it should be ensured that the influence of the external data sources and model specification is understood by performing scenario analyses surrounding the specification of the prior distributions. A summary of the relative advantages of informed Bayesian vs conventional models for some common tasks in HTAs is given in *Table 1*.

When these best practices are followed, Bayesian techniques have the potential to expedite patient access to novel therapies by enabling robust and transparent demonstration of the efficacy and value of novel therapies in data-deficient regimes where standard approaches are inadequate. Appropriate usage of Bayesian survival and cost-effectiveness models informed by historical study, real-world, or other external data has great potential to lead to more favorable healthcare decision-making for payers, manufacturers, and patients.

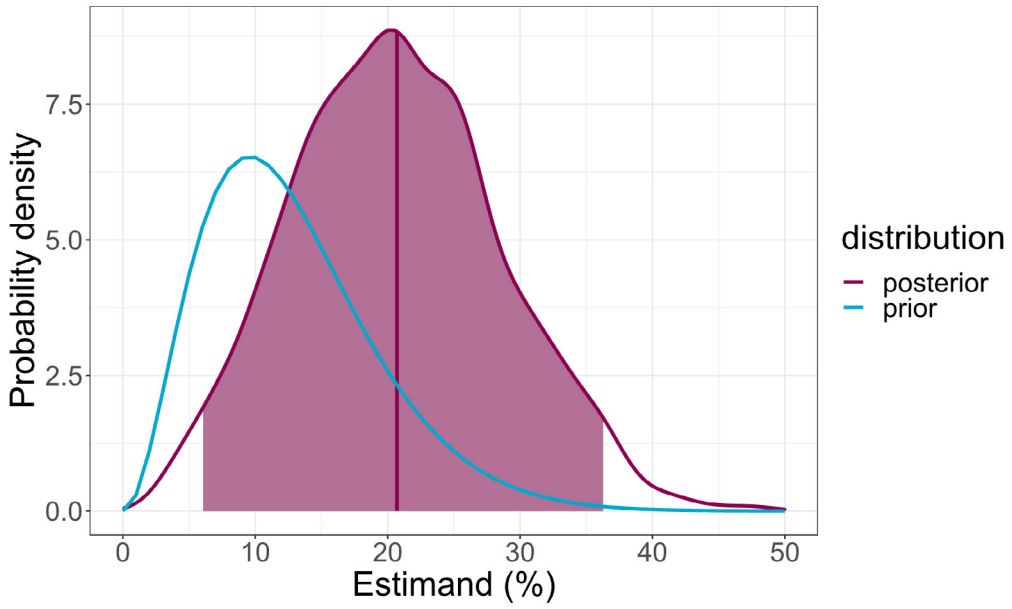

Figure 1: Schematic illustration of prior and posterior probability distributions for a model estimand. The vertical line shows the posterior mean, which is the Bayesian point estimate, and the shaded area shows the 95% credible intervals, which are the Bayesian analogue of 95% confidence intervals.

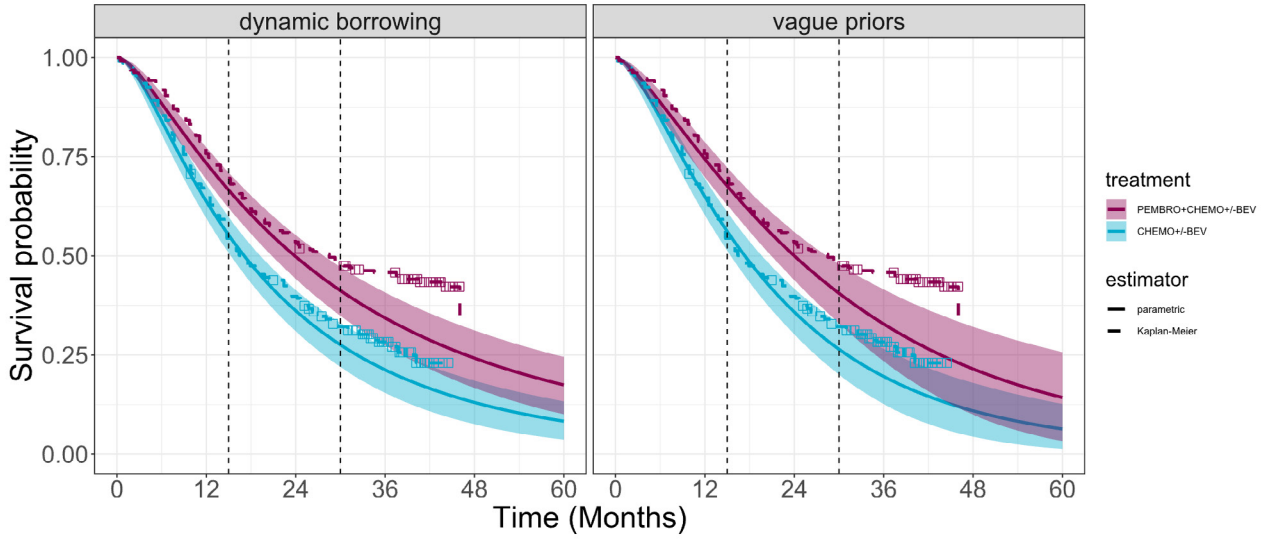

Figure 2: Application of a Bayesian dynamic borrowing model,[7] informed by historical control data, to reconstructed data from an interim analysis of the KEYNOTE-826 study in advanced cervical cancer, with 15 months minimum follow-up. Model predictions are compared to observations from the final analysis, with 30 months minimum follow-up. The Bayesian model yielded deliberately conservative estimates for the longer-term treatment effect, but achieved statistical significance where the uninformed (vague) model did not.[8]

Task	Bayesian models	Traditional models
Trial-based survival extrapolations	› May improve reliability of long-term predictions by invoking transparent assumptions based on prior data, avoiding naïve projections › Estimates the true decision uncertainty inclusive of existing available knowledge outside of the current study › Tailored to address limitations of individual studies and to investigate clinical hypotheses in particular patient populations	› May be sufficient (e.g., when data are mature, disease trajectories are not complex, longer-term survival is not a main driver of clinical- or cost-effectiveness, etc.) › Well-defined model selection algorithm outlined by regulators enforces consistency across submissions[11]
Subgroup analyses	› Can reduce uncertainty in estimates when sample sizes are small › Not predicated on a predefined significance level, consistent with exploratory nature of most subgroup analyses	› May be built into study design › Not contingent on availability of relevant external data, which may be difficult to source for specific patient subpopulations
Indirect treatment comparisons	› Can reliably fit more complex models (e.g., large networks of studies, flexible survival models, extrapolated outcomes) › Can reduce uncertainty in indirect treatment effect estimates when the network of studies is small › Can attenuate bias in comparative effect estimates arising from differences in follow-up duration between studies	› May be sufficient (e.g., moderate network sizes, based on simplistic quantities such as hazard ratios, etc.) › No requirement to assess model sensitivity to (vague) priors that are necessary in Bayesian models

Table 1: Summary of relative advantages of informed Bayesian vs traditional methods for some common tasks in health technology assessments and clinical evidence generation.

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