PharmacoEconomics
https://doi.org/10.1007/s40273-026-01645-w

PRACTICAL APPLICATION

Uncertainty in Economic Evaluation: A Pragmatic Guide for Health Technology Assessment (HTA) Agencies in Resource-Constrained Settings

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Received: 26 March 2026 / Accepted: 6 July 2026
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Abstract

Understanding the financial and health consequences if economic evaluation assumptions prove incorrect is essential for managing the risk associated with benefit package decisions, particularly in resource-constrained and overburdened healthcare systems. Yet these are also the settings that face the greatest challenges in conducting comprehensive uncertainty analysis, owing to a range of factors including limited skilled staff, data constraints, and short timelines to generate evidence in time to influence policy. This paper takes a pragmatic approach to support health technology assessment agencies in these settings to generate policy-relevant uncertainty analysis, drawing on good practice literature and the authors' collective experience conducting economic evaluation for policy across resource-constrained settings. For each step of the economic evaluation process, we outline the main sources of uncertainty, principles for deciding which uncertainty analysis to prioritise, and approaches to overcome some of the common challenges faced when dealing with constrained timelines, data, and skilled staff. The overarching goal is to support better-informed decisions, by targeting uncertainty analysis to factors that actually affect decisions and by effectively communicating this decision-relevant uncertainty to policymakers.

1 Introduction

Economic evaluations informing policy are inherently uncertain: data may be incomplete [1, 2], current practice poorly characterised [3], or stakeholders may disagree about how the technology will be implemented in practice [4, 5]. Uncertainty analysis aims to support better-informed decisions by assessing confidence in the results and identifying which sources of uncertainty could influence the most cost-effective intervention [6]. However, health technology assessment (HTA) agencies (or equivalent staff generating evidence to support policy recommendations) in resource-constrained settings are often challenged by limited time and expertise for comprehensive uncertainty analysis, even though the potential consequences of decisions are even more significant in these settings.

Economic evaluation guidelines for HTA address several types of uncertainty [7, 8], most often regarding data

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Published online: 23 July 2026

Key Points

Comprehensive uncertainty analysis is not always feasible for economic evaluations informing policy, especially in resource-constrained settings.

This paper outlines how to prioritise and adapt uncertainty analysis in these settings, emphasising pragmatic, decision relevant analysis and clear communication to policymakers.

inputs (e.g. confidence intervals, variability from random events, poor-quality data [1, 2, 9]), although uncertainty in the model structure and in the willingness to pay threshold are also increasingly addressed [9, 10]. Beyond uncertainty addressed by guidelines, analysts also face practical challenges that can undermine the usefulness of economic evaluations for policy. These include difficulty defining the decision question precisely [3], risk of misinterpretation by policymakers [11–13] and potential mismatch between what is modelled and how the intervention will be implemented in practice [4]. Given the multiple sources of uncertainty, the question becomes how to account for and communicate the consequences of this uncertainty to policymakers with limited time and resources [6, 14, 15].

The purpose of this paper is not to eliminate uncertainty, but to help analysts and policymakers identify which uncertainties actually affect decisions. This paper builds on other publications targeted at analysts conducting economic evaluations in resource-constrained settings [16–18] and is intended to apply to both rapid and full analysis. We assume the reader has a basic knowledge of the economic evaluation and uncertainty techniques presented in Table 1 but may face challenges in applying these techniques owing to limited timelines and short policy windows for change, insufficient funding for data collection or few staff with expertise in economic evaluation. Although comprehensive guidance on uncertainty analysis exists [2, 9, 19, 20], this paper explains what to prioritise and how to adapt when time, data and analytical capacity are constrained, as is often the case for economic evaluations to inform policy.

2 Guide Structure and Development

This manuscript is structured according to the typical steps of an economic evaluation, highlighting sources of uncertainty at each step (Table 2). Although both the CHEERS and CHEQUE checklists highlight the importance of understanding how uncertainty affects findings and decision-making [1, 21], in our experience this is seldom done in practice, especially in resource-constrained settings. There exists good practice reports for uncertainty

Table 1 Explanation of economic evaluation and uncertainty analysis terms used in this manuscript

Term	Explanation
Cost-effectiveness acceptability curve (CEAC)	Shows the probability that an intervention is the most cost-effective option at different willingness-to-pay thresholds, derived from PSA.
Cost-effectiveness threshold (CET)	An ICER value, or range of values, below which an intervention is considered to be cost-effective and above which it is not.
Deterministic sensitivity analysis (DSA)	Identifies whether the uncertainty range of a single parameter (one-way) or multiple parameters (multi-way) is great enough to affect the most cost-effective intervention in the analysis.
Incremental cost effectiveness ratio (ICER)	Compares the benefit and cost between the intervention and the next best comparable option, calculated as the difference in cost divided by the difference in benefit.
Probabilistic sensitivity analysis (PSA)	Quantifies how the combined uncertainty across all model parameters influences the probability that an intervention is cost-effective.
Scenario analysis	Identifies a set of alternative plausible scenarios and considers whether the most cost-effective intervention is different under each. Scenarios may vary assumptions about the future (e.g. epidemiology, patient profile), model structure (e.g. patient pathway), or best quality datasets (e.g. national hospital databases, clinical trials, meta-analyses), among others.
Threshold analysis	Determines the value of one or more parameters at which the most cost-effective intervention changes.
Value of information (VOI)	Estimates the monetary value of reducing uncertainty in an economic evaluation (either through further research or price negotiation). One of the main analyses is expected value of partial perfect information (EVPPI), which (1) identifies the parameters with uncertainty that is great enough to affect the most cost-effective intervention, and (2) estimates the monetary value of collecting better data for each of these parameters. The EVPPI can be compared with anticipated research costs to decide whether it is worth collecting more data (the expected value of sample information).

analysis [2, 9], how-to guides [20, 22] and tools to make the impact of uncertainty transparent [12, 23], as well as the iDSI reference case, which aims to improve the quality, consistency and transparency of economic evaluations for policy [24]. However, these resources provide more limited practical guidance on how to prioritise and conduct uncertainty analysis under real-world constraints such as limited data, technical capacity, and short policy timelines. This guide aims to complement, not replace, existing guidance by focusing specifically on pragmatic approaches for identifying decision-relevant uncertainty, prioritising analyses that are most likely to influence decisions, addressing common implementation challenges and communicating uncertainty effectively to policymakers.

General principles in each section draw on established guidance for economic evaluation [1, 2, 9, 21], good practice from the literature and the authors' collective experience conducting economic evaluation informing policy across low-income and middle-income countries (LMICs). We distinguish between essential analysis (the minimum to characterise decision-relevant uncertainty) and recommended analysis (additional analyses that strengthen the evidence where resources permit), based on the authors' collective judgement. All authors provided input on the following: (1) challenges encountered in addressing uncertainty in economic evaluation, (2) considerations unique to economic evaluations informing policy in resource-constrained settings, (3) good practice developed in their setting and (4) feasibility of implementing the proposed approaches. A full worked example is available in Supplement 1 and further reading and resources can be found in Table 3.

3 Decision Problem

Uncertainty in the decision problem occurs when there is difficulty defining the population, intervention, comparator, outcome (PICO) or other elements of the decision problem [3]. It is not only shaped by technical disagreement (for example, around current practice or how an intervention will be implemented), but also by political feasibility, procurement rules and implementation capacity, which influence how the PICO question is defined and the model structured [25, 26].

Within the economic evaluation literature, uncertainty in the decision problem is framed as a subjective methodological choice requiring justification [10]. Yet in resource-constrained settings, the decision problem is rarely a straightforward assessment of inserting a technology into a well-functioning system with high population coverage. To illustrate, in contexts with limited infrastructure and vertical donor funding, questions about quality of care, skilled workforce, programme scalability and sustainable financing may strongly influence the decision problem [27]. With incomplete coverage of essential benefit packages, decision questions have to account for gaps in the clinical pathway, while contexts constrained by existing coverage commitments may be concerned with expansion, substitution or reprioritisation, rather than the full set of optimal interventions. Across resource-constrained settings, the decision problem is further shaped by explicit or implicit budget ceilings: even for cost-effective interventions, uncertainty around eligible population, uptake or unit costs may create substantial financial risk for the payer.

The policy recommendation or implementation may diverge from what was modelled in an economic evaluation. By understanding the decision problem from the perspective of policymakers and implementers from the start, analysts can identify what these changes may be and whether they could affect the most cost-effective intervention. For example, if districts proceed with a different delivery strategy to reduce operational costs, does the intervention remain cost-effective? If policymakers are under pressure to fill a gap in the benefit package, the technology is very likely to be introduced regardless of cost-effectiveness – has the analyst mapped alternative interventions to include in the analysis for better informed policymaking?

3.1 General Principles

1. Consult with the decision-maker, implementers and other stakeholders to understand the purpose of the decision question, alternatives for the PICO question and implementation constraints that may affect costs and/or health impact [28, 29].
2. Justify why the final research question has been selected and run scenario analysis where possible [2, 10].
3. In the final report to policymakers, clearly report the following.
    i) The decision problem modelled and scenario analysis conducted, with justification [3].
    ii) Elements of the decision problem that may change the most cost-effective policy intervention [1, 2].

3.2 Approaches in Resource-Constrained Settings

Challenge 1: difficulty convening stakeholders within short policy timelines

If relevant stakeholders are geographically dispersed or have limited availability, solutions such as structured surveys, brief telephone interviews or asynchronous input through a shared document can be considered.

Table 2 Summary of steps to understand and communicate uncertainty in economic evaluations for policymaking.

Step	Source(s) of uncertainty	Essential	Recommended	What to report	What to communicate to policymakers (i.e. uncertainty that affects decisions)
Decision problem	Does the decision question account for different stakeholder views, on-the-ground implementation and policy constraints?	Finalise the decision question after discussion with key stakeholders around how the intervention will be implemented	Conduct scenario analysis (qualitatively or quantitatively) with alternative PICO questions and/or assumptions about implementation	The decision problem modelled, with justification, and the scenario analysis conducted	Factors related to the policy or its implementation that may change the most cost-effective intervention
Scope of the evaluation	Is the evaluation comparable to other economic evaluations used for policymaking in the country?	Ensure consistency in the discount rate, perspective and principles for choice of time horizon across economic evaluations	Vary the discount rate, time horizon and perspective in sensitivity analysis	1) Time horizon, discount rate, perspective 2) Costs included under the chosen perspective	Whether the selected time horizon, discount rate or perspective influences the most cost-effective intervention
Model structure	Does the model structure reflect key elements of context-specific clinical pathways and implementation?	Consider whether key uncertainties in model structure are likely to change the result	For important uncertainties, quantitively model whether a change in structure alters the most cost-effective option	Assumptions in the base case model structure	Aspects of model structure that could change the most cost-effective intervention
Data to populate the model	Is the data sufficiently representative and good enough quality to inform policy?	1) DSA 2) PSA (unless there is insufficient analytical capacity) 3) Alternative datasets (or extreme but plausible ranges) for data that are not representative or low quality	EVPPI	1) Upper and lower bounds for DSA 2) Distributions and shape parameters for PSA 3) Alternative datasets (or bounds) for low quality or unrepresentative data 4) EVPPI values above zero (or above a defined threshold)	1) Overall uncertainty in the data (from PSA) 2) Threshold values of parameters that change the most cost-effective intervention 3) Alternative datasets / plausible values that change the most cost-effective intervention 4) Benefit in collecting additional data or negotiating price
Use of outputs for policy	Do policymakers understand the implications of uncertainty analysis well enough to make an informed recommendation?	Explain the implications of uncertainty analyses for policy in clear and accessible language	Engage with policymakers regularly throughout the modelling process	Uncertainty that could change the most cost-effective option	N/A

DSA deterministic sensitivity analysis, *EVPPI* expected value of partial perfect information, *PSA* probabilistic sensitivity analysis

Table 3 Further reading and tutorials

Topic	Title	Reference
Overview of uncertainty analysis methods	Generating, presenting, and interpreting cost-effectiveness results in the context of uncertainty: a tutorial for deeper knowledge and better practice	[20]
	Accounting for methodological, structural and parameter uncertainty in decision-analytic models: a practical guide	[2]
	Model parameter estimation and uncertainty: a report of the ISPOR-SMDM modelling good research practices task force 6	[9]
Structural uncertainty	Model structuring for economic evaluations of new health technologies	[10]
Value of information (VOI)	A practical guide to value of information analysis	[77]
	ISPOR Value of Information Analysis Emerging Good Practices Task Force (Reports 1 and 2)	[60, 61]
	A guide to value of information methods for prioritising research in health impact modelling	[22]
	Value of information analysis in models to inform health policy	[14]
Confidence in the data (quantitative methods)	Bias modelling in evidence synthesis	[57]
	Methods to address confounding and other biases in meta-analyses: review and recommendations	[56]
Confidence in the data (qualitative methods)	Handbook for grading the quality of evidence and strength of recommendations using the GRADE approach	[78]

Challenge 2: limited staff time to scope scenarios

Guidelines from normative agencies (e.g. World Health Organization) or systematic reviews of economic evaluations can highlight aspects of the decision problem that may influence cost-effectiveness. For example, maternal pertussis vaccination has been found to be more cost-effective than cocooning across settings and is most cost-effective in settings with low DTP (diphtheria-tetanus-pertussis) vaccine coverage [32]. In this example, analysts could justify excluding cocooning from the analysis and hypothesise that maternal vaccination may become less cost-effective if DTP vaccination targets are met.

Challenge 3: insufficient time and resources to run extensive scenario analysis

Scenario analysis can be conducted qualitatively using problem structuring methods [33, 34]. Based on existing knowledge, analysts can arrange scenarios according to whether they have higher, similar or lower cost than the base case and conduct the same with health outcomes [34]. Without conducting an economic evaluation, this can indicate which scenarios could be more or less cost-effective than the base case. Prior to model development, this can prioritise data collection or shortlist which scenario analysis to conduct. After model development, it highlights which scenarios may change the most cost-effective intervention.

3.2.1 Example: HPV Vaccination

There is evidence that out-of-school girls have higher baseline risk of HPV infection and cervical cancer, yet they are also less likely to be vaccinated [31]. Despite this, a model may assume equivalent risk of HPV exposure in vaccinated and unvaccinated girls owing to limited time and data, overestimating the benefit of vaccination. Therefore, if the base case result is cost-effective but very close to the cost-effectiveness threshold, it may be concluded that vaccination is unlikely to be cost-effective unless equitable vaccination coverage of high-risk girls is achieved.

3.2.2 Example: Kidney Replacement Therapy

For an economic evaluation of a peritoneal dialysis (PD) first policy in India, it was noted that the guidelines differed from real-world implementation of the current dialysis policy [30]. The authors therefore analysed scenarios with different comparators for (i) current dialysis utilisation and (ii) full implementation of a dialysis access scheme. The results showed that a PD-first policy would be cost saving in both scenarios, with greater savings realised if the guidelines were fully implemented (−54,025 INR/QALY compared with −408,918 INR/QALY).

4 Scope of the Evaluation

The scope of the economic evaluation includes the perspective (for example, societal or payer), discount rate, and time horizon selected [19]. Without guidelines to standardise the scope of the evaluation across studies, the results of the economic evaluation can differ owing to subjective choices of the analyst and research team [6, 35]. This problem is

particularly acute for perspective, as definitions of what is included under a given perspective can differ (for example, inclusion of productivity costs under societal perspective) [17, 18, 36, 37]. This is known as methodological uncertainty, which good practice recommends addressing through adherence to national guidelines [2, 9].

4.1 General Principles

1. As far as possible, ensure consistency across economic evaluation studies used for policymaking and transparent reporting of the discount rate, time horizon and perspective (including which costs were included under the perspective) [1, 21].
2. Conduct sensitivity analysis to identify whether the discount rate, time horizon, or perspective influences the most cost-effective intervention [2, 21]. If it does, communicate the conditions under which the most cost-effective intervention changes to policymakers.

4.2 Approaches in Resource-Constrained Settings

Challenge 4: absence of national guidelines for economic evaluation

A number of approaches may be taken to ensure consistency across studies in the absence of country-specific guidelines. These include borrowing guidelines from other countries, following standard practice from other economic evaluations to inform policy in the country, adopting a discount rate from the literature or from the treasury [39, 40], or following good practice by using a lifetime horizon [19]. The International Decision Support Initiative reference case was developed to provide guidance to analysts working in settings without national guidelines and provides an overview of general principles for setting the perspective, discount rate and time horizon [24].

4.2.1 Example: HPV Vaccination

For HPV vaccination, the main benefits and cost savings may occur 30-40 years after vaccination, therefore the chosen discount rate often influences whether or not vaccination is cost-effective [38]. In communicating the sensitivity analysis results to decision-makers, a low discount rate may be framed as 'if we value future health benefit and cost savings from preventive (as opposed to curative) measures' and the high discount rate framed as 'if we place greater value on the health benefit and cost savings that can be achieved now'.

4.2.2 Example: Kidney Replacement Therapy

An economic evaluation comparing dialysis modalities in Canada varied the discount rate and time horizon to consider the impact on results. Although the ICER value of each intervention varied in the analysis, the relative cost-effectiveness of each intervention stayed constant, increasing confidence in the results: 'Over a range of discount rates and time horizons, the relative ordering of incremental costs remained the same with small differences observed' [41].

5 Model Structure

Whether the model structure is fit for purpose depends on how much we know about the cause-effect relationships and model states [6]. Structural uncertainty considers whether model structure and functions reflect the disease, clinical pathway, or health system being modelled [3]. This includes overall model architecture represented in the model diagram (e.g. choice of health states, transition structure) and functional assumptions, such as the technique for extrapolating survival beyond observed trial data.

Structural uncertainty is particularly relevant in the context of adaptive HTA, in which a model is adopted from another setting or a simplified model is developed [42, 43]. When adapting models from other settings, differences in disease epidemiology, costing structures, health system organisation and treatment patterns introduce structural uncertainty [44, 45], which remains even if the model is able to reproduce baseline data (e.g. number of cases).

Good practice recommends parameterising structural uncertainty, by assigning a probability to alternative model structures and including this probability as a parameter in sensitivity analysis [9, 10, 46]. The probability distribution for each model structure may be informed by data but most often depends on expert opinion [10, 47].

5.1 General Principles

1. Consider alternative model structures that could have been selected and understand the impact of these structures on the most cost-effective intervention [1]. The aim is not to exhaust all possible model structures (which would be unfeasible under policy timelines), but to assess whether plausible alternatives could realistically change the decision.
2. Prioritise fitness-for-purpose of the model: a simpler model that captures the main cost and outcome drivers for the specific context and decision problem may be preferable to a complex structure that does not reflect the context-specific decision problem, clinical pathways and implementation realities, or cannot be adequately parameterised. The simpler the model, the lower the likelihood of errors [48]. Steps for model transparency and validation (described elsewhere [48]) can support

policymakers and subject matter experts to evaluate how closely the model represents reality.
3. Identify whether additional data could increase confidence in the most cost-effective intervention. If structural uncertainty has been parameterised, this may be through value of information (VOI) analysis [9]. Otherwise, indicate whether any uncertainty in model structure could change the most cost-effective intervention.

5.2 Approaches in Resource-Constrained Settings

Challenge 5: reliance on models from other settings

In settings that are still building capacity for economic evaluation, models are often adapted from international studies. Structural assumptions embedded in the original model, such as treatment pathways, adherence, quality of care or follow-up intensity, may lead to structural uncertainty in terms of whether the model reflects local clinical practice. In these contexts, engaging local clinicians and programme managers to validate care pathways is essential to reduce decision risk. It can also be helpful to review differences between model structures in the published literature, to better understand the assumptions in the chosen model structure.

Challenge 6: insufficient time to develop multiple model structures

Problem structuring methods can indicate whether model structure assumptions may change the most cost-effective intervention [33, 34]. The research team can list out key uncertainties in model structure and consider the impact on costs and health outcomes relative to the base case. Take, for example, a new diabetes drug that is cost-effective in the base case. A key structural uncertainty may be around whether the drug also reduces rate of heart failure. Including heart failure as a separate state would likely increase the absolute benefit of the intervention and health system cost savings, making the drug even more cost-effective. This uncertainty is therefore unlikely to change the conclusion in this example. It should be noted, however, that qualitative problem structuring cannot quantify magnitudes and may miss interactions between variables, so is best used to identify when further analysis is needed.

Challenge 7: insufficient data/expertise to parameterise alternative model structures

Analysts can calculate the ICER for each model structure to identify whether the most cost-effective intervention remains the same [10]. If the most cost-effective intervention is different for alternative model structures, further data collection or stakeholder discussion can indicate which structure may be a closer representation of reality. For example, clinical experts can review whether disease progression pathways in the model match observed patterns while national and local programme managers can verify implementation assumptions.

Challenge 8: limited time or expertise for validation of model structure

Certain steps can be taken for model validation even with limited resources. Regular stakeholder engagement can review the face validity of model structure, whether it accurately reflects the stated problem, and whether model outputs are in line with expectations [48]. Similarly, analysts can conduct extreme values testing and scenario analysis to check whether the test results are consistent with what would be expected [48]. In settings building the analytical capacity of staff, asking two analysts to independently develop parts of the model can identify errors or unclear assumptions to articulate and check with stakeholders.

5.2.1 Example: HPV Vaccination

Many settings do not have the capacity for dynamic transmission modelling and may evaluate cost-effectiveness of HPV vaccination with a static model. Static models cannot account for changes in transmission rates and may therefore underestimate benefit from herd immunity. If vaccination is already cost-effective with a static model, it is likely cost-effective with a dynamic transmission model. However, if it is not cost-effective, more information may be needed regarding herd effects.

5.2.2 Example: Kidney Replacement Therapy

The face validity of a model to evaluate donor allocation for kidney transplant was evaluated by comparison with the literature and stakeholder review: ‘The model structure and assumptions used were validated by a systematic review and by two clinical experts involved in kidney transplantation care’ [49].

An economic evaluation of PD-first in India tested the external validity of the model by comparison of model outputs with epidemiological data: ‘Our model estimates show the overall survival for CKD patients with PD at 5 and 7 years to be 39.5 and 26.3%, respectively, similar to studies by Prasad et al. and Lasfar et al. that reported similar long-term survival of 39% at 5 years and 30% at 7 years’ [30].

6 Data to Populate the Model

There are three main types of uncertainty associated with model parameterisation: (1) inherent randomness (stochastic uncertainty); (2) measurement error, captured through confidence intervals (parameter uncertainty); and (3) confidence in the data, comprising data quality and representativeness [6, 13, 50–53]. Stochastic uncertainty is most relevant for patient-level models such as microsimulation, agent-based

modelling or discrete-event simulation [9] and will not be discussed in this article.

Parameter uncertainty is most often accounted for through sensitivity analysis, which may be deterministic (one-way or multi-way) or probabilistic (see Table 1 for an explanation of each) [2, 9]. Although deterministic sensitivity analysis (DSA) can be a good starting point to understand the data, it does not show the impact of total parameter uncertainty [54]. Probabilistic sensitivity analysis (PSA) captures the combined effect of uncertainty across all parameters simultaneously, including correlations and interactions between parameters that one-way DSA cannot reflect [1, 9]. Uncertainty in data quality or representativeness is commonly addressed through qualitative analysis (for example, GRADE for effectiveness estimates), although methods have been developed to parameterise data quality [55–57].

6.1 General Principles

1. Conduct both DSA and PSA where possible [9]. From a policymaking perspective, whether uncertainty causes results to cross a decision threshold is more important than the magnitude of the ICER change. Clearly report whether uncertainty changes the most cost-effective option, to align uncertainty analysis more closely with policy deliberations and decision-making.
2. DSA: The most important information for policymaking is whether uncertainty in any of the parameters could change the most cost-effective intervention. When conducting DSA, shortlist any parameter (or combination of parameters for multi-way DSA) that changes the most cost-effective intervention. For each shortlisted parameter, conduct a threshold analysis to identify the value at which the most cost-effective policy intervention changes. Communicate these threshold values to policymakers in an understandable way, for example: 'vaccination is cost-effective if incidence is higher than 10 per 1,000 population, which is only possible if we believe that less than 10% hospitalised cases are being reported in the national surveillance system'. When reporting DSA results as a tornado diagram, show the decision threshold and all parameters whose DSA results cross the threshold – this is more informative for policymaking than ranking parameters according to the absolute change in ICER.
3. PSA: The results from PSA are often shown on an ICER plane, with the results from each simulation shown in a scatter plot. The appropriate number of PSA simulations can be calculated for a given confidence level (e.g. 9604 simulations for 95% confidence that the median is within the 49th-51st percentile [6]), or by increasing the number of simulations until the results converge (i.e. the PSA result remains stable when the PSA is repeated multiple times). For PSA, it is important to communicate the percentage of simulations where the most cost-effective intervention is the same as the base case. For example, 'changing eligibility criteria for haemodialysis is more cost-effective than current practice in 55% of simulations, meaning we are unsure whether the intervention is cost-effective'.
4. Value of information (VOI): Expected value of partial perfect information (EVPPI) analysis can highlight which sources of parameter uncertainty may change the most cost-effective intervention, at a given willingness-to-pay threshold [58]. When conducting EVPPI, report any non-zero values, as these represent the parameters for which it may be worth collecting additional data. In a situation in which many parameters have non-zero values, selecting only those with the highest EVPPI value can be most helpful to shortlist data collection needs for policymakers. If the policymaker can request further research or delay a decision, recommend further research for any parameters where the anticipated cost of data collection is less than the EVPPI value [59]. Otherwise, VOI results can still be used pragmatically to recommend price negotiation, managed entry agreement or conditional listing to reduce decision risk [60, 61].
5. Data quality or representativeness: Identify any parameters with low-quality or non-representative data [1], and conduct scenario analysis with an alternative data set. For example, if effectiveness has been taken from a local clinical trial, scenario analysis can use data from a systematic review. Report any scenario analysis that changes the most cost-effective intervention, alongside the main strengths and limitations of each dataset.

6.2 Approaches in Resource-Constrained Settings

Challenge 9: administrative data is incomplete or fragmented across providers

Where primary cost data are unavailable, analysts may rely on tariffs, procurement prices or small facility studies. In such cases, threshold analysis around unit costs can be particularly informative for payers, as it directly links price levels to affordability and value.

Challenge 10: missing data ranges for DSA or lack of alternative datasets

When there is no confidence interval or alternative data set, expert opinion can help to define 'plausible limits'. Guidance exists for structured expert elicitation [62, 63]. While informal methods may also be used with transparent

documentation of which experts were engaged, how, and why, it can be helpful for analysts to refer to the cited references to understand potential biases of informal expert elicitation techniques. It is not recommended to prioritise specific parameters for DSA, as the number of parameters has minimal impact on speed of analysis. Analysts should avoid arbitrary confidence intervals (e.g. ±20% of the base value) as they tie DSA results to magnitude of the base value and do not represent actual uncertainty in parameter values [29].

Challenge 11: missing probability distributions for PSA

There is established guidance outlining which probability distributions are appropriate for which parameter types (for example, beta distribution for probabilities, gamma for costs and length of stay, log-normal for relative risks) [9]. If the shape parameters for the distribution are missing, they can be estimated on the basis of plausible ranges for the parameter, using wider confidence intervals to avoid overconfidence in results [6]. If in doubt, the assigned probability distributions can be varied in sensitivity analysis to see whether they influence the most cost-effective option [6].

Challenge 12: low computing power to run an adequate number of simulations for PSA

If there is limited computing power to run multiple simulations, Latin Hypercube Sampling (LHS) can be used instead of random sampling in PSA to analyse global uncertainty across all parameters, as it gives stable results with a smaller number of simulations [64].

Challenge 13: lack of expertise to conduct PSA

If full probabilistic analysis cannot be conducted, multiway DSA can vary multiple parameters at one time to build a sense of the impact of global uncertainty (although it should be noted that this approach will show the most extreme plausible values and therefore may overstate uncertainty compared to PSA).

Challenge 14: lack of expertise to conduct VOI

Freely available, peer-reviewed online tools such as Sheffield Accelerated Value of Information (SAVI) can be used to calculate the EVPPI directly from the PSA results [65, 66].

Challenge 15: no defined threshold for VOI

In settings without an explicit cost-effectiveness threshold, analysts can use supply side threshold estimates for their country in the literature [67], apply implicit thresholds from past decisions (an ICER value that seems to indicate whether an intervention is introduced or not), or apply thresholds from local studies (where available). If time permits, re-running the VOI with alternative threshold values can show the extent to which willingness-to-pay affects the importance of missing or poor-quality information.

6.2.1 Example: HPV Vaccination

An important input for HPV vaccination transmission models is sexual contact matrices, but country-specific data may come from a very small unrepresentative sample. In this case, sensitivity analysis may use contact matrices from neighbouring countries with shared culture and similar HPV prevalence. If vaccination is cost-effective with one dataset but not with others, this should be communicated to policymakers, so they can discuss which dataset is more applicable or invest in further research.

6.2.2 Example: Kidney Replacement Therapy

Uncertainty analysis results from an economic evaluation of pre-emptive kidney transplantation in Thailand were communicated in the following way to show the decision significance of results [68]:

- DSA—'The sensitivity analyses demonstrated robustness of the model as [living relative kidney transplant] remained cost-saving within the varied ranges of all input parameters.'
- PSA—'Most of the plots (86.2%) of incremental cost versus incremental QALY of pre-emptive [living relative kidney transplant] versus non-pre-emptive [deceased donor kidney transplant] were below the [cost-effectiveness threshold]. Of these, 79.4% was considered cost-saving (the plots were in the right lower quadrant of the plane).'

7 Interpreting Results

To decide whether an intervention is cost-effective, the ICER is commonly compared to a cost-effectiveness threshold (CET), which reflects system efficiency or willingness to pay [69]. Especially in resource-constrained settings, different willingness-to-pay thresholds may exist across government payers and donors. Even with commonly agreed, empirically determined CETs, there is uncertainty in measurement of the CET value [69, 70]. To account for CET uncertainty, the cost-effectiveness acceptability curve (CEAC), on the basis of results from a PSA, is commonly used in economic evaluation to show how willingness to pay affects the most cost-effective intervention. A tutorial for generating and communicating a CEAC may be found elsewhere [20].

7.1 General Principles

1. Explicitly state and justify the decision threshold used to determine whether the ICER is cost-effective.
2. Generate a CEAC to show uncertainty in the decision threshold, to identify whether the intervention with the highest probability of being cost-effective changes within a plausible range of willingness-to-pay thresholds.
3. Clearly communicate the implications to policymakers. For example: 'There is 70% probability that the procedure is cost-effective at the CET published in our guidelines. However, at the cost-effectiveness threshold suggested by a recently published supply side threshold estimate, probability that the procedure is cost-effective drops to 30%. This means that introducing the procedure may lead to a net loss of health. We therefore recommend price negotiation to reduce decision risk.'

7.2 Approaches in Resource-Constrained Settings

Challenge 16: no established CET

Without an established CET, policymakers may struggle to know which part of the CEAC is most relevant. In this case, reference values can be provided for policymakers to understand which part of the curve to focus on. For example: 'On the chart we have highlighted the implicit willingness-to-pay for past decisions taken by this committee and an estimate from the literature of the supply-side threshold for our country, representing current efficiency of the health system, or how much benefit we currently get from the investment we put into the health sector. The CEAC shows that adjunct technology X has the highest probability of being cost-effective at all willingness-to-pay values within this range, meaning that we have high confidence that introducing this adjunct technology will improve the health benefit realised for every dollar that we invest in our health system'.

Challenge 17: lack of expertise to generate a CEAC

If a CEAC cannot be generated, scenario analysis using alternative CET values, such as supply-side estimates in the literature [67] or historical implicit thresholds from past decisions, can show whether conclusions depend on the assumed opportunity cost.

7.2.1 Example: Kidney Replacement Therapy

In an evaluation of donor allocation for kidney transplant in Australia, different allocation options were compared against two different willingness to pay thresholds. The probability of each option being cost-effective remained the same at both thresholds, increasing confidence in the recommended option: 'Separate analysis was conducted against two different WTP thresholds, AUD 42,000/QALY and AUD 67,000/QALY to assess the sensitivity of the results. Neither of the WTP values changed the [relative order] of the different allocation options' [49].

8 Communicating Uncertainty

Different stakeholders have different educational backgrounds and training, which can affect how information is heard and understood [50, 51, 53]. The way in which uncertainty is communicated can therefore affect quality of input from stakeholders throughout the economic evaluation process, as well as whether policymakers are able to effectively use uncertainty analysis results to inform policy. In settings where HTA processes are newly established, economic evaluations may play a dual role in both informing decisions and building institutional understanding of economic evidence. In these contexts, standardised summary formats and repeated use across decisions can gradually improve decision-maker familiarity with uncertainty concepts. Iterative engagement reinforces concepts from uncertainty analysis, promotes dialogue between the analyst and policymaker around which uncertainty is most relevant for decision-making, and builds confidence in the model, making policymakers more willing to act despite uncertainty rather than delaying decisions indefinitely [71, 72].

8.1 General Principles

1. Communicate, in non-technical terms, what each source of uncertainty means for decision-making. If analysts cannot articulate why a particular uncertainty matters or under what circumstances it would change the recommendation, then the uncertainty analysis—or how it is communicated—is not fit for purpose.
2. Include a structured summary table at the start of the report that highlights which sources of uncertainty may change the most cost-effective intervention. For example:
3. 'High uncertainty in disease incidence: if true incidence is greater than 25 per 100,000 (i.e. less than 20% cases are reported through the national surveillance system), the intervention becomes cost-saving.'
4. 'Quality of services: if resource constraints lead to dialysis sessions being shortened to less than 3 hours (as is the case in most public hospitals currently), increasing number of reimbursable dialysis sessions is not cost-effective.'
5. Promote iterative engagement with policymakers. Analysts are responsible for identifying and communicating uncertainty transparently, while policy-

makers are responsible for weighing that uncertainty against urgency, feasibility, and societal values. Iterative engagement improves the quality of dialogue so that policymakers are better able to use the results from uncertainty analysis.

8.2 Approaches in Resource-Constrained Settings

Challenge 18: low understanding of economic evaluation among policymakers

Understanding of economic evaluation can be developed over time by using standardised formats to present the results of economic evaluation studies, explaining the results from the study in accessible terms, and holding regular meetings for policymakers to ask questions [73, 74].

Challenge 19: limited policymaker availability for iterative engagement

Frequent short discussions can build greater understanding than a single long meeting at the end of the study, and will help to identify which uncertainties are of greatest concern to the policymaker [15, 74]. Alternatively, if policymakers are not available, engaging with the policy secretariat (focal points responsible for managing the operations of a policy process, however, formal or informal it may be) on a regular basis can give insight into policymaker concerns and build capacity of the secretariat as a knowledge translator between the analyst and policymakers [75].

9 Discussion

Conducting extensive uncertainty analysis can be impractical within the time constraints of economic evaluations to inform policy [76]. However, failing to account for uncertainty may give a false sense of confidence in the results and miss the opportunity to understand which factors could affect the most cost-effective intervention [6, 9]. For countries moving towards universal health coverage, the key risk is not uncertainty itself, but making high-commitment coverage decisions without understanding the financial and health consequences if assumptions prove incorrect.

There are several limitations to this work. The challenges and recommendations have been developed based on the authors' collective experience, with no systematic mapping of the literature or validation through structured techniques such as Delphi. This decision was taken because we believed the main challenges encountered are often not documented, but it does mean that the guidance cannot claim to capture the experience of every setting. In terms of generalisability, we emphasised LMIC settings, and although our experience is that the challenges are broadly generalisable to high-income resource-constrained settings, the decision problem uncertainty may be less relevant. Our illustrative examples are also concentrated in two clinical areas, HPV vaccination and kidney replacement therapy, chosen for the depth of the authors' experience in them. However, the principles are intended to be generalisable.

Perhaps most importantly, we have laid out approaches to overcome system constraints. There is a risk that these approaches will be seen as easier alternatives to investing in capacity and stronger HTA institutions. However, in our experience stronger HTA systems are built once policymakers see the value of economic evaluation for their decisions. By building capacity to target analysis to the most policy relevant aspects of a decision, this manuscript supports the longer-term goal of developing stronger HTA institutions. The approaches laid out in this document should therefore be seen as temporary measures while capacity is being strengthened, and not as viable long-term alternatives.

10 Summary

In this manuscript, we describe how analysts can use uncertainty analysis, whether sophisticated quantitative methods or estimates based on existing knowledge, to identify which sources of uncertainty could change the most cost-effective intervention and to communicate this to policymakers in accessible terms. While comprehensive uncertainty analysis remains the methodological ideal, the approaches outlined here offer pragmatic alternatives that can improve the transparency and usefulness of economic evaluations even with significant resource constraints. Our focus has been not on prescribing ideal methods, but on guiding analysts on what to prioritise and how to adapt when comprehensive analysis is not feasible. The key principle throughout is to focus on decision relevance and to make the analysis useful to policymakers. The goal is not perfection, but rather honest characterisation of what is known, what is uncertain and what would need to be true for a different intervention to be preferred.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40273-026-01645-w.

Acknowledgements The Health Intervention and Technology Assessment Program (HITAP) Foundation, based in Thailand, supports evidence-informed priority-setting and decision-making for healthcare. HITAP is funded by national and international public funding agencies.

Declarations

Funding This study was funded by the National Science, Research and Innovation Fund (NSRF) through the Program Management Unit for Human Resources & Institutional Development, Research and Innovation [B41G670025 & B41G680024]. The funders had no role in the design, data collection, analysis, interpretation, or writing of the report. HCT acknowledges funding from the MRC Centre for Global Infectious Disease Analysis (reference MR/R015600/1), jointly funded by

the UK Medical Research Council (MRC) and the UK Foreign, Commonwealth & Development Office (FCDO), under the MRC/FCDO Concordat agreement and is also part of the EDCTP2 programme supported by the European Union.

Author Contributions All authors contributed to conceptualisation of the manuscript. The first draft of the manuscript was written by Siobhan Botwright and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Competing interests The authors have no competing interests to declare that are relevant to the content of this article.

Data Availability We do not analyse or generate any datasets.

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