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The professional society for health economics and outcomes research

Improving healthcare decisions

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November 2, 2026

Dear Health Economics Methods Advisory (HEMA):

ISPOR—The Professional Society for Health Economics and Outcomes Research – is pleased to respond on behalf of its membership to your consultation titled **"Methods to Analyze and Present Uncertainty in Economic Evaluation to Support HTA Decisions."**

ISPOR is a scientific and educational society with many of its members engaged in evaluating health technologies, including pharmaceuticals, medical devices, and other interventions. ISPOR membership includes nearly 18,000 individual and chapter members from more than 100 countries worldwide. The number of individual members in the US exceeds 2,500. Our membership is uniquely diverse and represents a variety of stakeholder perspectives, including research organizations, academia, payers, patient groups, government, healthcare professionals, health technology assessment bodies, and the life sciences industry. ISPOR also publishes peer-reviewed scientific journals, develops internationally recognized Good Practices Reports, and convenes scientific conferences to communicate healthcare evidence to decision makers worldwide. We note and appreciate the reference to several relevant ISPOR reports in your draft guidance.

The response to this consultation was led by the ISPOR Scientific Initiatives Team and Chief Science Officer Laura Pizzi. Comments were solicited from ISPOR's Global Access to Medical Innovation and Statistical Methods in HEOR Special Interest Groups, Patient Council, Patient-Centered Research Community of Interest, Health Science and Policy Council, Health Technology Assessment Council, and other members. The attached document summarizes our comments on specific provisions of the guidance.

ISPOR would be happy to answer any questions about our response, serve as a partner, or participate in any follow-up consultations on the relevant items mentioned in the document.

Sincerely,

Robert M. Abbott
CEO & Executive Director
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Beth Devine, PhD, PharmD, MBA, MSc
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Methods to Analyze and Present Uncertainty in Economic Evaluation to Support HTA Decisions

On behalf of its members, ISPOR, the professional society for health economics and outcomes research, welcomes the Health Economics Methods Advisory (HEMA) draft report, which offers a useful framework for identifying, analyzing, communicating, and considering uncertainty in health technology assessment (HTA). ISPOR members identified four themes for HEMA's consideration: decision-focused approaches to uncertainty; assumptions and limitations of uncertainty analysis; practical application and communication of uncertainty; and patient values, outcome risk, and equity considerations. ISPOR also strongly supports integrated evidence generation informed by early dialogue between innovator companies and HTA, regulator, payer, and patient representatives to reduce uncertainty before the decision is at hand.

Decision-focused approaches to uncertainty

ISPOR members support the report's decision-focused approach. Members value the expanded decision menu and the emphasis on matching potential responses to the source of uncertainty, rather than to its magnitude alone.

Members recommend that the report present managed access, coverage with evidence development, pricing arrangements, and additional research as options to consider rather than prescriptive responses. The appropriate choice depends on whether uncertainty is reducible, the value and feasibility of further research, population size, and decision context; the practicality of each option also varies across HTA systems.

Members also suggest that the report clarify which value-of-information (VOI) measures suit which research decisions. Expected value of perfect information (EVPI) sets an upper bound on the value of resolving the uncertainty analyzed, but it does not show whether that uncertainty was avoidable or whether further research is feasible. For a specific proposed study, expected value of sample information (EVSI) and expected net benefit of sampling (ENBS) may be more informative because they reflect the information the study could generate and its cost.

Assumptions and limitations of uncertainty analysis

Members emphasized that the report should state clearly that probabilistic sensitivity analysis (PSA), VOI analysis, and related methods are conditional on the evidence, model structure, parameters, and uncertainties they represent. Accordingly, ISPOR recommends replacing "probability of an incorrect decision," which could be read too broadly, with "probability that another option has higher net benefit, given the uncertainties represented."

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Members also cautioned against double counting—reflecting the same evidentiary limitation through multiple adjustments without justification. ISPOR recommends adding a principle against double counting to the report's minimum reporting expectations.

Because not all uncertainties can or should be quantified—and even a comprehensive PSA cannot capture every source—members suggest that HEMA reconsider terms such as "full integration," which may imply otherwise, and prioritize further integration where uncertainty could materially affect the decision.

Members further noted that assumptions translating model results into decisions—the value of a unit of health, the decision objective or maximand, and the healthcare budget—should be distinguished from uncertainty in the underlying evidence or model. Where a recommendation is sensitive to the cost-effectiveness threshold, HEMA could present net benefit and VOI across a relevant range of thresholds.

HEMA may also wish to consider Chaudhary and colleagues' review and guide to evaluating uncertainty in health economic models.[1]

Practical application and communication of uncertainty

ISPOR members support the report's taxonomy of uncertainty sources and its structured uncertainty assessment. The assessment could play a greater role in implementation by documenting each uncertainty's source, decision relevance, reducibility, handling, and potential responses.

Assigning each material uncertainty a consistent identifier across the technical analysis, committee materials, and public summary would also improve traceability and help flag double counting.

Members suggest that managed access and other evidence-generation arrangements specify the uncertainty addressed, data requirements, responsibilities, reassessment plans, and handling of inconclusive evidence. These arrangements should also account for research feasibility, particularly where population size or other constraints limit study design.

Public-facing statements should distinguish model or evidence scenarios from patient-level outcomes and note that probability and expected-loss estimates are conditional on the uncertainties analyzed; without this context, technical results may mislead.

Finally, because analytical capacity and decision processes differ across HTA settings, HEMA could distinguish core practices from conditional or advanced approaches and provide worked examples, templates, or checklists.

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Patient values, outcome risk, and equity considerations

Members support involving patients and caregivers in identifying omitted outcomes, treatment and research burden, care pathways, consequences of delayed access, heterogeneity in benefits and harms, and other considerations that economic models may not adequately capture. The report could further clarify how this input informs both the decision framework and the communication of uncertainty.

Members also raised several open questions: how to separate financial risk to healthcare payers from variation in individual patients' health outcomes, whether expected net-health-benefit approaches fully reflect preferences regarding outcome risk, and how disease severity should be incorporated when weighing the consequences of decision errors. Given these questions, HEMA could distinguish recommendations for current practice from areas requiring further methodological research, such as patient and societal risk preferences and the role of severity within expected-loss frameworks.

Where populations are underrepresented in the evidence or findings may not transfer across subgroups, the report should identify these limitations and their implications so that these considerations remain visible to decision makers.

ISPOR appreciates the opportunity to comment and welcomes continued engagement with HEMA as the report is finalized.

ISPOR acknowledges members from the Statistical Methods in HEOR and Global Access to Medical Innovation Special Interest Groups and the Health Science Policy Council for their assistance in assembling these comments, along with ISPOR staff Clarissa Cooblall, Scientific Initiatives Senior Director, and Claire Brindley, Scientific Initiatives Manager.

References

1. Chaudhary MA, Chu H, Cappelleri JC. Evaluating uncertainties in health economic models: a review and guide. *Appl Stoch Models Bus Ind*. 2025;41:e70044. doi:10.1002/asmb.70044