

## Letter

**Cite this article:** Grimm SE, Pouwels XGLV, Ramaekers BLT, Wijnen B, Grutters J, Joore MA (2023). Response to “UNCERTAINTY MANAGEMENT IN REGULATORY AND HEALTH TECHNOLOGY ASSESSMENT DECISION-MAKING ON DRUGS: GUIDANCE OF THE HTAi-DIA WORKING GROUP”. *International Journal of Technology Assessment in Health Care*, **39**(1), e70, 1–3  
<https://doi.org/10.1017/S026646232300260X>

Received: 16 August 2023  
Accepted: 10 September 2023




### Keywords:

uncertainty; health technology assessment; healthcare decision-making; healthcare policy; managed entry agreements

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# Response to “UNCERTAINTY MANAGEMENT IN REGULATORY AND HEALTH TECHNOLOGY ASSESSMENT DECISION-MAKING ON DRUGS: GUIDANCE OF THE HTAi-DIA WORKING GROUP”

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With great interest, we read the article entitled “Uncertainty Management in Regulatory and Health Technology Assessment Decision-Making on Drugs: Guidance of the HTAi-DIA Working Group” by Hogervorst et al. (1). We wish to commend HTAi, DIA, and the Working Group for selecting this important topic.

To our surprise, the guidance only references a small subset of the extensive work on the topic of uncertainty in and outside of health technology assessment (HTA). Not referenced were articles on considerations around uncertainty in health (2–7), classifications of uncertainty in HTA (8–11) and outside HTA (12–16), and methods for uncertainty assessment (17–22), among others. For a scientific article in a scientific journal, methods and results of the scoping review are not described in sufficient detail. It remains unclear if and how the state of the art on uncertainty in HTA was used to develop the guidance.

Specifically, the part on “building blocks comprising decision-making uncertainty” bears non-negligible similarity to published work that is identified in the authors’ scoping review but not cited – the TRUST tool 2020 (11). TRUST considers the same uncertainty factors as outlined in the present article, including origin (location in TRUST), type (source in TRUST), impact/risk (same in TRUST), and relevance/judgment (appraisal in TRUST). The types of actionable uncertainty considered are also very similar: inaccurate (separated into imprecision, bias, and indirectness in TRUST); unavailable (same in TRUST); and non-understandable (transparency in TRUST). In line with existing classifications of uncertainty (8;16), TRUST also considers uncertainty stemming from methodological issues. TRUST does not include uncertainty from conflicting information, as this was considered to be reflected through imprecision or bias (4). TRUST is readily available, validated, practical, and used in practice (e.g., in Dutch Healthcare Institute reports). It is unclear how the presented guidance improves upon this.

There is an opportunity to build upon the challenges other researchers in the area of uncertainty assessment in and outside of HTA have identified and the methods proposed to address these. The progress made on the following topics has not been sufficiently covered in the guidance, including but not limited to:

- uncertainty identification, for example, using the TRUST tool (11) and other methods (6;18);
- uncertainty analysis methods including Bayesian methods (23), value of information (24–26), structured expert elicitation (27;28), and incorporation of difficult to quantify uncertainty (29–33);
- uncertainty communication (17;34–36);
- link between uncertainty and evaluation of managed entry agreement (MEA) schemes (36–39);
- uncertainty (in)tolerance in regulatory and HTA decision-making (3;40–42).

As a next step, the Working Group refers to the link of their proposed framework with mitigation strategies. Importantly, there are existing frameworks and tools covering this topic including frameworks for classifications of different MEA schemes (43;44), and approaches for assessing MEAs (36;39;45). We urge the Working Group to consider and transparently build upon these, where relevant.

To conclude, we agree with the HTAi-DIA Working Group that uncertainty is a fundamental component of decision-making. We argue that collaboration with experts in the abovementioned topics and thorough, transparent reviews of the literature to build upon the wealth of existing knowledge will make the resulting guidance stronger.

**Funding statement.** This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

**Competing interest.** All authors of this letter are also authors of the article “Development and Validation of the TRansparent Uncertainty ASsessmentT (TRUST) Tool for Assessing Uncertainties in Health Economic Decision Models” (11) that is mentioned in this letter.

## References

- Hogervorst MA, Vreman R, Heikkinen I, et al. Uncertainty management in regulatory and health technology assessment decision-making on drugs: Guidance of the HTAi-DIA Working Group. *Int J Technol Assess Health Care*. 2023;39:e40.
- Claxton K. Exploring uncertainty in cost-effectiveness analysis. *Pharmacoeconomics*. 2008;26:781–798.
- Grutters JP, van Asselt MB, Chalkidou K, Joore MA. Healthy decisions: Towards uncertainty tolerance in healthcare policy. *Pharmacoeconomics*. 2015;33:1–4.
- Bilcke J, Beutels P, Brisson M, Jit M. Accounting for methodological, structural, and parameter uncertainty in decision-analytic models: A practical guide. *Med Decis Making*. 2011;31:675–692.
- Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics*. 2000;17:479–500.
- Annemans L, Makady A. TRUST4RD: Tool for reducing uncertainties in the evidence generation for specialised treatments for rare diseases. *Orphanet J Rare Dis*. 2020;15:127.
- Kalke K, Studd H, Scherr CL. The communication of uncertainty in health: A scoping review. *Patient Educ Couns*. 2021;104:1945–1961.
- Briggs AH, Weinstein MC, Fenwick EA, et al. Model parameter estimation and uncertainty: A report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6. *Value Health*. 2012;15:835–842.
- Stevenson M, Tappenden P, Squires H. Methods for handling uncertainty within pharmaceutical pricing decisions. *Int J Sys Sci*. 2014;45:60–68.
- Silva EN, Silva MT, Pereira MG. Uncertainty in economic evaluation studies. *Epidemiol Serv Saude*. 2017;26:211–213.
- Grimm SE, Pouwels X, Ramaekers BLT, et al. Development and validation of the TRansparent Uncertainty ASsessmentT (TRUST) tool for assessing uncertainties in health economic decision models. *Pharmacoeconomics*. 2020;38:205–216.
- Walker WE, Harremoes P, Rotmans J, et al. Defining uncertainty: A conceptual basis for uncertainty management in model-based decision support. *Integr Assess*. 2003;4:5–17.
- van Asselt MBA, Rotmans J. Uncertainty in integrated assessment modelling: From positivism to pluralism. *Clim Change*. 2002;54:75–105.
- van der Bles AM, van der Linden S, Freeman ALJ, et al. Communicating uncertainty about facts, numbers and science. *R Soc Open Sci*. 2019;6:181870.
- Lofstedt R, Boudier F. Evidence-based uncertainty analysis: What should we now do in Europe? A view point. *J Risk Res*. 2021;24:521–540.
- Bouwknegt M, Havelaar A. Uncertainty assessment using the NUSAP approach: A case study on the EfoNAO tool. EFSA Supporting Publications; 2015. EN-663.
- Wolff HB, Qendri V, Kunst N, Alarid-Escudero F, Coupe VMH. Methods for communicating the impact of parameter uncertainty in a multiple-strategies cost-effectiveness comparison. *Med Decis Making*. 2022;42:956–968.
- Otten TM, Grimm SE, Ramaekers B, Joore MA. Comprehensive review of methods to assess uncertainty in health economic evaluations. *Pharmacoeconomics*. 2023;41:619–632.
- Scholte M, Marchau V, Kwakkel JH, et al. Dealing with uncertainty in early health technology assessment: An exploration of methods for decision making under deep uncertainty. *Value Health*. 2023;26:694–703.
- Petersohn S, Grimm S, Ramaekers BLT, ten Cate-Hoek AJ, Joore M. Exploring the feasibility of comprehensive uncertainty assessment in health economic modeling: A case study. *Value Health*. 2021; doi:10.1016/j.jval.2021.01.004.
- Claxton K, Sculpher M, McCabe C, et al. Probabilistic sensitivity analysis for NICE technology assessment: Not an optional extra. *Health Econ*. 2005;14:339–347.
- Mauskopf J. Multivariable and structural uncertainty analyses for cost-effectiveness estimates: Back to the future. *Value Health*. 2019;22:570–574.
- Nixon RM, O'Hagan A, Oakley J, et al. The rheumatoid arthritis drug development model: A case study in Bayesian clinical trial simulation. *Pharm Stat*. 2009;8:371–389.
- Fenwick E, Steuten L, Knies S, et al. Value of information analysis for research decisions – An introduction: Report 1 of the ISPOR value of information analysis emerging good practices task force. *Value Health*. 2020;23:139–150.
- Rothery C, Strong M, Koffijberg HE, et al. Value of information analytical methods: Report 2 of the ISPOR value of information analysis emerging good practices task force. *Value Health*. 2020;23:277–286.
- Heath A, Manolopoulou I, Baio G. A review of methods for analysis of the expected value of information. *Med Decis Making*. 2017;37:747–758.
- Bojke L, Soares M, Claxton K, et al. Developing a reference protocol for structured expert elicitation in health-care decision-making: A mixed-methods study. *Health Technol Assess*. 2021;25:1–124.
- Ayers D, Cope S, Towle K, et al. Structured expert elicitation to inform long-term survival extrapolations using alternative parametric distributions: A case study of CAR T therapy for relapsed/refractory multiple myeloma. *BMC Med Res Methodol*. 2022;22:272.
- Strong M, Oakley JE, Chilcott J. Managing structural uncertainty in health economic decision models: A discrepancy approach. *J R Stat Soc Ser C Appl Stat*. 2012;61:25–45.
- Le QA. Structural uncertainty of Markov models for advanced breast cancer: A simulation study of lapatinib. *Med Decis Making*. 2016;36:629–640.
- Ghabri S, Cleemput I, Josselin JM. Towards a new framework for addressing structural uncertainty in health technology assessment guidelines. *Pharmacoeconomics*. 2018;36:127–130.
- Afzali HH, Karnon J. Exploring structural uncertainty in model-based economic evaluations. *Pharmacoeconomics*. 2015;33:435–443.
- Jackson CH, Bojke L, Thompson SG, Claxton K, Sharples LD. A framework for addressing structural uncertainty in decision models. *Med Decis Making*. 2011;31:662–674.
- Alarid-Escudero F, Enns EA, Kuntz KM, Michaud TL, Jalal H. “Time traveling is just too dangerous” but some methods are worth revisiting: The advantages of expected loss curves over cost-effectiveness acceptability curves and frontier. *Value Health*. 2019;22:611–618.
- Eckermann S, Briggs A, Willan AR. Health technology assessment in the cost-disutility plane. *Med Decis Making*. 2008;28:172–181.
- Grimm SE, Pouwels X, Ramaekers BLT, et al. State of the ART? Two new tools for risk communication in health technology assessments. *Pharmacoeconomics*. 2021;39:1185–1196.
- Pouwels X, Grutters JPC, Bindels J, Ramaekers BLT, Joore MA. Uncertainty and coverage with evidence development: Does practice meet theory? *Value Health*. 2019;22:799–807.
- Makady A, van Veelen A, de Boer A, et al. Implementing managed entry agreements in practice: The Dutch reality check. *Health Policy*. 2019;123:267–274.
- Grimm SE, Strong M, Brennan A, Wailoo AJ. The HTA risk analysis chart: Visualising the need for and potential value of managed entry agreements in health technology assessment. *Pharmacoeconomics*. 2017;35:1287–1296.
- van Asselt M, Vos E. Wrestling with uncertain risks: EU regulation of GMOs and the uncertainty paradox. *J Risk Res*. 2008;11:281–300.
- Wranik WD, Gambold L, Peacock S. Uncertainty tolerance among experts involved in drug reimbursement recommendations: Qualitative evidence from HTA committees in Canada and Poland. *Health Policy*. 2021;125:307–319.
- Salcher-Konrad M, Naci H, Davis C. Approval of cancer drugs with uncertain therapeutic value: A comparison of regulatory decisions in Europe and the United States. *Milbank Q*. 2020;98:1219–1256.

43. **Walker S, Sculpher M, Claxton K, Palmer S.** Coverage with evidence development, only in research, risk sharing, or patient access scheme? A framework for coverage decisions. *Value Health.* 2012;15:570–579.
44. **Garrison LP Jr, Towse A, Briggs A,** et al. Performance-based risk-sharing arrangements-good practices for design, implementation, and evaluation: Report of the ISPOR good practices for performance-based risk-sharing arrangements task force. *Value Health.* 2013;16:703–719.
45. **Grimm S, Strong M, Brennan A, Wailoo A.** *Framework for analysing risk in health technology assessments and its application to managed entry agreements.* Sheffield: University of Sheffield; 2016.