ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

505 LAWRENCE SQUARE BLVD SOUTH
LAWRENCEVILLE, NJ 08648

P +1-609-586-4981
F +1-609-586-4982

info@ispor.org
www.ispor.org

June 6, 2023

Docket Number: OMB-2022-0014

Dear the Office of Management and Budget (OMB):

ISPOR – the professional society for health economics and outcomes research (HEOR) - is pleased to respond on behalf of its membership to your consultation entitled "Regulatory Analysis."

ISPOR is a scientific and educational society with many of its members engaged in evaluating health technologies, including pharmaceuticals, medical devices, and other interventions. We have a large membership spanning 110 countries globally, across a range of disciplines, including health economics, epidemiology, public health, pharmaceutical administration, psychology, statistics, medicine, and more, from a variety of stakeholder perspectives, such as the life sciences industry, academia, research organizations, payers, patient groups, government, and health technology assessment bodies. The research and educational offerings presented at our conferences and in our journals are relevant to many of the issues and questions raised in this request for information.

The response to this consultation was led by the Policy Outlook Committee of our most senior advisory body, the Health Science Policy Council. We solicited our general membership for comments. The attached document provides both summary and line-by-line responses based on their comments. We hope they prove useful.

ISPOR would be happy to answer any questions about our response, and to participate in any follow-up consultations on the relevant program items mentioned within the report.

Sincerely,

Robert Abbott
CEO & Executive Director
ISPOR

ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

505 LAWRENCE SQUARE BLVD SOUTH
LAWRENCEVILLE, NJ 08648

P +1-609-586-4981
F +1-609-586-4982

info@ispor.org
www.ispor.org

ISPOR Comments on OMB Circular A-4

ISPOR would like to compliment OMB on presenting a thorough and rigorous guidance on use of benefit-cost analysis (BCA) for regulatory actions. ISPOR membership expertise lies in health economics and outcomes research, especially for but not limited to assessment of single technologies such as pharmaceuticals and medical devices. It involves extensive use of cost-effectiveness analysis (CEA) and net monetary benefit analysis (essentially benefit-cost analysis) and often takes a societal perspective, so this guidance is highly relevant to our methods, although our emphasis tends to be more on CEA than BCA. Also, our focus is generally cost-effectiveness at the individual level rather than a summary population-level assessment of benefits vs costs and often do not consider program-level costs.

Your full guidance covers a much broader range of programs and interventions than ISPOR's expertise in health-related services allows us to comment on. Thus, we have limited our comments to three main areas most relevant to our own work – value assessment; use of real-world data, especially for causal inference; and discount rates - along with a minor comment.

On issues related to value assessment:
In the 60 years since Nobel laureate Kenneth Arrow's seminal AER article[1] on the importance of understanding the role of uncertainty in medical care, health economists have endeavored to bring a full appreciation of this feature to their analyses. Because so much of medical care is either purchased in price-regulated markets, eg, for physician and hospital services, or under insurance coverage, analysts are reluctant to accept provider charges or administered prices as indicative of the true value of health benefits or their true social opportunity costs.

Beginning about 50 years ago, an approach evolved in health economics to support comparisons across different technologies using CEA or its subtype called cost-utility analysis (which uses the cost-per-quality-adjusted life year [QALY] gained as its core metric). It has long been pointed out that given a valuation of a QALY gain, applying a "CE threshold" value per QALY, CEA is nearly equivalent to CBA. Two prestigious panels of methodological experts (First Panel, 1996[2]; Second Panel, 2016[3]) have endorsed cost-utility analysis for medical interventions, and nearly 12,000 such studies have been completed and are catalogued in an inventory database.[4]

Yet, this methodology has had and still has its critics, especially in relation for the potential for discrimination against disabled patients. More recently, ISPOR established a "Special Task Force" (STF) to examine the recent proliferation of US value frameworks motivated by concerns about perceived high and rising drug prices. Among its six recommendations, one[5] was viewed as being especially important and is relevant to this submission:

"ISPOR Special Task Force Recommendation II (of VI): Base health plan coverage and reimbursement decisions on an evaluation of the incremental costs and benefits of healthcare technologies as is provided by cost-effectiveness analysis.

1. Cost-per-QALY analyses have strengths and limitations
2. Frameworks that focus on coverage/reimbursement should consider cost per QALY, as a starting point

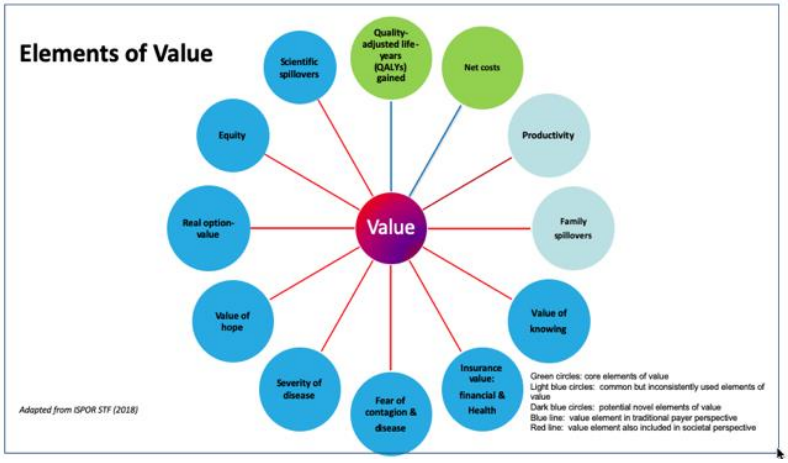
---

[1] Arrow KJ. Uncertainty and the welfare economics of medical care. 1963. *Bull World Health Organ*. 2004;82(2):141-149.
[2] Weinstein MC, Russell LB, Gold MR, Siegel JE. *Cost-Effectiveness in Health and Medicine*. Oxford university press; 1996.
[3] Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA*. 2016;316(10):1093-1103. doi:10.1001/jama.2016.12195
[4] Neumann PJ, Garrison LP, Willke RJ. The History and Future of the "ISPOR Value Flower": Addressing Limitations of Conventional Cost-Effectiveness Analysis. *Value Health*. 2022;25(4):558-565. doi:10.1016/j.jval.2022.01.010
[5] Garrison LP, Neumann PJ, Willke RJ, et al. A Health Economics Approach to US Value Assessment Frameworks-Summary and Recommendations of the ISPOR Special Task Force Report [7]. *Value Health*. 2018;21(2):161-165.

505 LAWRENCE SQUARE BLVD SOUTH
LAWRENCEVILLE, NJ 08648
P +1-609-586-4981
F +1-609-586-4982
info@ispor.org
www.ispor.org

3. Consider elements not normally included in CEAs (eg, severity of illness, equity, risk protection) but more research needed."

This STF outlined some 10 additional "elements of value" beyond the QALY gains and net cost impact and called it "augmented" CEA.[6] These categories were not meant to represent the definitive parsing of value, rather were intended to suggest where further research is needed. This has come to be illustrated by what is called the "ISPOR Value Flower".



The two green petals were meant to represent conventional CEA. The light blue petals for productivity and family spillovers represent a broader "societal" perspective of non-health sector impacts on society and family members. Moving clockwise, the next six petals represented effects related to uncertainty: the "value of knowing" related to diagnostic interventions, the value of insurance that provides peace of mind from protection against illness events with their adverse impact on QALYs and medical costs; greater severity of illness increases the utility gains from health improvements; therapies that provide a substantial chance of a cure can yield additional "value of hope"; and treatments that extend life provide the "real option value" to benefit from future, as yet unknown, advances. Medical innovations may also operate at a societal level to improve "health equity" across vulnerable population subgroups. Also, scientific advances can create knowledge spillovers or externalities that support a learning health care system through cross-cutting advances, such as artificial intelligence or through the success and failures of trials of competing technologies.

Since the STF published its report, work has continued on each of these elements of value. Perhaps the most notable has been the work of Charles Phelps and Darius Lakdawalla to formalize the definition and estimation of insurance value and the value of hope via "Generalized Risk-Adjusted Cost-Effectiveness Analysis"—the GRACE method.[7] This work supports the case for a variable CE threshold across different interventions that would argue for higher thresholds for conditions with more severe illness or disability, thereby potentially addressing concern about QALY related discrimination. And, perhaps somewhat coincidentally, the varying impact of COVID-19 on different subpopulations has led to a great deal of new interest and work on health equity, which has been formalized via "Distributional CEA" (DCEA).[8,9] There has

[6] Lakdawalla DN, Doshi JA, Garrison LP, Phelps CE, Basu A, Danzon PM. Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report [3]. *Value Health*. 2018;21(2):131-139. doi:10.1016/j.jval.2017.12.007
[7] Lakdawalla DN, Phelps CE. Health Technology Assessment With Diminishing Returns to Health: The Generalized Risk-Adjusted Cost-Effectiveness (GRACE) Approach. *Value Health*. 2021;24(2):244-249. doi:10.1016/j.jval.2020.10.003
[8] Cookson R, Mirelman AJ, Griffin S, et al. Using Cost-Effectiveness Analysis to Address Health Equity Concerns. *Value Health*. 2017;20(2):206-212. doi:10.1016/j.jval.2016.11.027
[9] Cookson R, Griffin S, Norheim OF, Culyer AJ, Chalkidou K. Distributional Cost-Effectiveness Analysis Comes of Age. *Value Health*. 2021;24(1):118-120. doi:10.1016/j.jval.2020.10.001

505 LAWRENCE SQUARE BLVD SOUTH
LAWRENCEVILLE, NJ 08648
P +1-609-586-4981
F +1-609-586-4982
info@ispor.org
www.ispor.org

also been recent research on the real option value[10] and scientific spillovers.[11]

In light of our comments above, we recommend that evaluation of any regulatory action affecting individual or population health recognize the potential benefits that go beyond the simple health gains as represented in the value of statistical life (VSL), value of statistical life-year (VSLY), or QALY.

<u>On use of real-world data:</u>
Given the importance of the quantification of benefits and costs in a BCA, we were surprised not to find a section of the guidance devoted to this topic, particularly for cases when they may be estimated from observational (individual) data analysis. Perhaps the reason is the fact that causal inference has been a major focus of econometrics, statistical, epidemiologic, and related literature for many years makes it a daunting topic to cover. Nevertheless, some reference to that literature and "recent" advances in research design seemed called for (eg, Angrist et al 2010).[12] In that vein, we would like to mention the progress being made with target trial emulation, where the research design seeks to mimic a randomized controlled trial in terms of patient characteristics, time of initiating the "treatment", and other critical trial characteristics. While mainly applied in health care to date, there is no reason it could not be applied, as the natural experiment approach is, in other settings. A seminal reference to the method here is Hernan and Robins 2016[13], while a recent study showing how target trial emulation can successfully replicate randomized-controlled trial (RCT) results is Wang et al 2023.[14]

More generally, the use of real-world data for estimating "treatment effects" involves a wide range of considerations related to the quality and credibility of the results. These issues can be informed by a number of ISPOR Good Practices reports on comparative effectiveness research (CER), including these topics:

i. Defining, reporting, and interpreting[15]
ii. Bias and confounding in the design[16]
iii. Causal inference[17]
iv. Transparency[18] and replicability (joint with ISPE)[19]
v. Assessing relevance and credibility[20]

---

[10] Li M, Basu A, Bennette C, Veenstra D, Garrison LP. How Does Option Value Affect the Potential Cost-Effectiveness of a Treatment? The Case of Ipilimumab for Metastatic Melanoma. *Value Health*. 2019;22(7):777-784. doi:10.1016/j.jval.2019.02.002
[11] Xie RZ, Towse A, Garrison LP. Should We Pay for Scientific Knowledge Spillovers?: The Underappreciated Value of "Failed" R&D Efforts. *Int J Technol Assess Health Care*. Published online March 17, 2022:1-17. doi:10.1017/S0266462322000150
[12] Angrist, Joshua D., and Jörn-Steffen Pischke. 2010. "The Credibility Revolution in Empirical Economics: How Better Research Design Is Taking the Con out of Econometrics." Journal of Economic Perspectives 24 (2): 3–30.)
[13] Hernan, Miguel A., Robins, James M. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *American Journal of Epidemiology*, Volume 183, Issue 8, 15 April 2016, Pages 758–764, https://doi.org/10.1093/aje/kwv254
[14] Wang, Shirley V., Schneeweiss, Sebastian, and the RCT-DUPLICATE Initiative. Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses Results of 32 Clinical Trials. JAMA. 2023;329(16):1376-1385. doi:10.1001/jama.2023.4221
[15] Berger ML, Mamdani M, Atkins D, Johnson ML. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report—part I. Value Health. 2009;12(8):1044-1052.
[16] Cox E, Martin BC, Van Staa T, Garbe E, Siebert U, Johnson ML. Good research practices for comparative effectiveness research: approaches to mitigate bias and confounding in the design of non-randomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force–parn II. Value Health. 2009;12(8):1053-1061.
[17] Johnson ML, Crown W, Martin BC, Dormuth CR, Siebert U. Good research practices for comparative effectiveness research: analytic methods to improve causal inference from nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report--Part III. *Value Health.* 2009;12(8):1062-1073.
[18] Berger ML, Sox H, Willke RJ, et al. Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. *Pharmacoepidemiol Drug Saf.* 2017;26(9):1033-1039.
[19] Wang SV, Schneeweiss S, Berger ML, et al. Reporting to Improve Reproducibility and Facilitate Validity Assessment for Healthcare Database Studies V1.0. *Pharmacoepidemiol Drug Saf.* 2017;26(9):1018-1032.
[20] Berger ML, Martin BC, Husereau D, et al. A questionnaire to assess the relevance and credibility of observational studies to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health.* 2014;17(2):143-156.

ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

505 LAWRENCE SQUARE BLVD SOUTH
LAWRENCEVILLE, NJ 08648

P +1-609-586-4981
F +1-609-586-4982

info@ispor.org
www.ispor.org

We believe it would be useful for this guidance to provide additional guidance on the process and methods for estimating policy action effects from observational data.

On issues related to discounting:
As background, the HEOR field routinely uses time discounting in our evaluations. Different countries prefer to use different discount rates, based on different conceptual approaches and/or empirical evidence, but the most common rate used is 3%.

Firstly, the OMB proposes using an updated social rate of time preference of 1.7%, based on updated empirical evidence. This makes sense to us both as an estimate, and for the use of an opportunity cost-based estimate, but we recognize the need for more research on the subject, given some thoughts below.

Secondly, there is a case for health-related benefits to be treated differently to normal consumption benefits. As stated on p77, the Ramsey equation tells us that the social rate of time preference is made up of two effects – pure time preference and a wealth effect, with the latter comprising the marginal utility of consumption multiplied by the expected growth rate of per capita consumption.

There is a good argument that the diminishing marginal utility of consumption element of discounting should not apply to life years, as set out in the UK government guide, which states, "the diminishing marginal utility associated with higher incomes does not apply as the welfare or utility associated with additional years of life will not decline as real incomes rise" (HM Treasury, 2022, Appendix 6, paragraph A6.16, p118)[21]. It argues for using a discount rate that only uses the pure social time preference rate, and so is lower than the standard social time preference rate.

Thirdly, differential discounting of costs and health benefits may be appropriate if budgets for health expenditure are constrained. There is an extensive literature on this, notably Claxton et al. (2011)[22]; Basu and Ganiats (2017)[23], Paulden et al. (2017)[24] and Claxton et al. (2019)[25].

In summary, while we recognize the merits of OMB's proposed social rate of time preference, we encourage consideration of alternative discounting of health benefits in appropriate situations.

Minor comment:
In your section on CEA you rightly comment that average cost-effectiveness (CE) ratios should be used with care and that an action with the lowest CE ratio may not be the best option. However, it may be worth noting that the lowest CE ratio does generally represent the best use of the resources involved, ie, the best rate of return, assuming the effectiveness measure is relevant across all options. A "bigger" program that uses more resources may have a larger net benefit but may not be the most efficient use of the resources involved.

Finally, ISPOR would like to acknowledge Lou Garrison and Adrian Towse for their assistance in assembling these comments.

---

21 HM Treasury, 2022. The Green Book Central Government Guidance on Appraisal and Evaluation. Available at https://www.gov.uk/government/publications/the-green-book-appraisal-and-evaluation-in-central-governent/the-green-book-2020
22 Claxton, K., Paulden, M., Gravelle, H., Brouwer, W. and Culyer, A.J., 2011. Discounting and decision making in the economic evaluation of health-care technologies. Health economics, 20(1), pp.2–15.
23 Basu A and Ganaits TG (2017). Discounting in Cost-Effectiveness Analysis. Chapter 10 in Neumann, P.J., et al., eds. Cost-Effectiveness in Health and Medicine. Oxford University Press, 2017.
24 Paulden M, O'Mahony JF, McCabe C. Discounting the Recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine. Pharmacoeconomics. 2017 Jan;35(1):5-13. doi: 10.1007/s40273-016-0482-0. PMID: 27943173.
25 Claxton K, Asaria M, Chansa C, Jamison J, Lomas J, Ochalek J, Paulden M. Accounting for Timing when Assessing Health-Related Policies. J Benefit Cost Anal. 2019 Jan 26;10(Suppl 1):73-105. doi: 10.1017/bca.2018.29. PMID: 33282628; PMCID: PMC7691758.