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Dear Dr. Seshamani,

ISPOR – the professional society for health economics and outcomes research (HEOR) - is pleased to respond on behalf of its membership to your consultation “**Medicare Drug Price Negotiation Program: Initial Memorandum, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2026, and Solicitation of Comments.**”

ISPOR is a scientific and educational society with many of its members engaged in evaluation of health technologies, including pharmaceuticals, medical devices, and other interventions. Established in 1995, ISPOR is a not-for-profit organization and the leading source for scientific conferences, peer-reviewed and MEDLINE®-indexed publications, good practices guidance, education, collaboration, and tools/resources in the HEOR field. We have a large membership living and working in 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. To engage our membership, we created a survey where their comments on different sections of the Memorandum could be recorded. We recognize that the Inflation Reduction Act (IRA) gives Secretary the option to consider a variety of different factors as part of the negotiation. Most of our members would strongly support consideration of “[t]he extent to which such drug represents a therapeutic advance as compared to existing therapeutic alternatives and the costs of such existing therapeutic alternatives.” We have less consensus on the other suggested factors, but we will leave to it those individual members to submit their detailed comments on those. We chose to provide comments in the areas most related to our scientific expertise, which is represented in part by an extensive set of Good Practices and similar reports (<https://www.ispor.org/heor-resources/good-practices>). Our comments are summarized in six major points below.

1. **CMS definition of unmet need.** Section 1194(e)(2) of the Act directs CMS to consider evidence about alternative treatments to the selected drug, as available, including, “the extent to which the selected drug and the therapeutic alternatives to the drug address unmet medical needs for a condition for which treatment or diagnosis is not addressed adequately by available therapy.” However, in the memorandum (p. 51), it is stated that “CMS will consider whether the selected drug fills an unmet medical need, which CMS intends to define as treating a disease or condition in cases where very limited or no other treatment options exist.”

We believe that this narrower interpretation of unmet need, while perhaps easier to identify and implement, may disadvantage some therapies where, despite available treatment and interventional options, a substantial burden of disease remains and significant healthcare (therapeutic, diagnostic, preventative) innovations are needed. Heart disease and cancer are still the leading causes of mortality¹ despite many treatments that improve outcomes. The actual burden of disease includes both direct and indirect factors beyond mortality, including loss of functionality, pain, mental illness, and sensory deficits (ie, quality of life deficits, as well as effects on caregivers, etc). In addition, the negative impact of these diseases on quality of life can be measured via disease-specific utilities, which are readily available² but absent from the definition of unmet need. Neurological diseases are additional examples where treatments may exist, such as for Parkinson's disease, but the unmet medical need is still high, and the value of addressing such unmet need should be clearly reflected in the Maximum Fair Price (MFP). Most new products are supported by burden of illness studies and updated research should support MFP negotiation.

2. **Comparative effectiveness.** “Comparative effectiveness of the selected drug and its therapeutic alternatives” is clearly a key consideration in MFP determination and we fully support CMS in its plan to use real-world evidence (RWE) in this area. We would like to make a few points here:
- 1) RWE will complement randomized clinical trial (RCT) data, clinical guidance, and expert consultation (including manufacturers and patients) in determining the most relevant therapeutic alternatives. RWE can indicate which alternatives are most used in general, as well as in different clinical situations (often including different indications) or key subpopulations.
 - 2) While recognizing the recent guidance from the FDA and other bodies relating to RWE, evaluating the quality of the research generating RWE can also be informed by a number of ISPOR Good Practices reports on comparative effectiveness research (CER), including these topics:
 - i. Defining, reporting, and interpreting³
 - ii. Bias and confounding in the design⁴
 - iii. Causal inference⁵
 - iv. Transparency⁶

¹ Xu JQ MS, Kochanek KD, Arias E. Mortality in the United States, 2021, NCHS Data Brief, no 456. In: National Center for Health Statistics, ed. Hyattsville, MD 2022.

² Cost-Effectiveness Analysis (CEA) Registry. The Center for the Evaluation of Value and Risk in Health 2023.
<https://cear.tuftsmedicalcenter.org/>.

³ 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.

⁴ 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—part II. *Value Health*. 2009;12(8):1053-1061.

⁵ 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.

⁶ 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.

- v. Replicability (joint with the International Society for Pharmacoepidemiology [ISPE])⁷
 - vi. Assessing relevance and credibility⁸
- 3) Different studies will yield different results, so evidence synthesis is likely to be necessary to generate a primary estimate of the difference in effect (with the recognition that uncertainty is present). Methods such as network meta-analysis and indirect treatment comparisons may be important here, and ISPOR has also created several Good Practices Reports on this topic:
- i. Interpretation⁹
 - ii. Conduct¹⁰
 - iii. Assessing relevance and credibility¹¹
3. **Value considerations.** Translating comparative effectiveness to fair pricing involves an assessment of the value of treatment effects, since pricing needs to be fair not only within a disease area, where CER can provide answers, but also across diseases, where CER does not. Value of treatment to patients and society involves several factors, probably most important of which is the clinical benefit per se, but other factors can be important as well. The delineation and estimation of those factors has been described recently by ISPOR¹² and by the Second Panel on Cost-Effectiveness in Health and Medicine,¹³ among others. Factors that are based on value to individuals include severity of disease, insurance value, value of hope, real option value, family spillovers, and others. CMS is well-positioned to also take into account factors that have broader value to society, such as productivity loss/gain, scientific spillovers, health equity, and others noted in ISPOR's "Value Flower" and in the Second Panel's Impact Inventory. While measurement of some of these factors is an evolving science, good progress¹⁴ is being made and it is presently feasible to take many of them into account.
4. **Measuring clinical benefit.** The exact metric for capturing clinical benefit in value calculations that includes not only survival gains but also quality of life improvements, has been a matter of considerable

⁷ 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.

⁸ 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.

⁹ Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health.* 2011;14(4):417-428.

¹⁰ Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value Health.* 2011;14(4):429-437.

¹¹ Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health.* 2014;17(2):157-173.

¹² Lakdawalla DN, Doshi JA, Garrison LP, Jr., 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.

¹³ Neumann PJ, Ganiats TG, Russell LB, Sanders GD, Siegel JE. *Second Panel on Cost-Effectiveness in Health and Medicine.* Oxford University Press; 2016.

¹⁴ 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.

debate.¹⁵ The IRA legislation forbids the use of the most standard measure, quality-adjusted life-years (QALYs), to the extent it gives relatively lower value to the extension of life of older, disabled, or terminally individuals. We do not believe that in most cases use of QALYs will disadvantage those groups since incremental QALY gain between treatments is the actual benefit measure and typically those groups will be represented in both treatment and comparator groups. The focus on treatment-based gains in quality of life is in fact generally more likely to benefit these groups since they tend to have lower quality of life ratings prior to treatment.

However, in cases where the value of treatment that extends survival in an older, disabled, or terminally ill population is being compared to the value of treatment to a more general population, alternative measures can be used such as equal value of Life Years Gained (evLYG),¹⁶ health years in total (HYT),¹⁷ and the generalized risk-adjusted QALY (GRA-QALY)¹⁸. Extended discussions of the use of QALYs relative to these alternative measures can be found in recent or forthcoming articles.^{19,20,21} In short, we recommend that CMS work with ISPOR and other expert groups in this area to settle on the most feasible approach to including both survival and quality of life gains in a clinical benefit measure for use in value calculations.

5. **Qualitative approach.** To provide some structure to the “qualitative” approach that CMS intends to use to adjust the MFP starting point for other clinical and value-based considerations, we recommend two considerations.

First, it is useful to have a single value construct to aggregate different factors influencing the value of treatment. The standard cost/QALY metric used by many countries and other groups does not easily capture all value elements and is of course based on the QALY measure. An ISPOR task force on value assessment suggested several such aggregate measures.²² One approach is a specific deliberative process called multi-criteria decision analysis (MCDA) that results in a single value construct; ISPOR has

¹⁵ Owerhohle S. Could a fight over cost-effectiveness upend Medicare drug price negotiation before it's begun? *Stat.* 2023. <https://www.statnews.com/2023/03/28/qaly-medicare-negotiation-drugs/>. Accessed April 12, 2023.

¹⁶ Institute for Clinical and Economic Review. Cost-Effectiveness, the QALY, and the evLYG. <https://icer.org/our-approach/methods-process/cost-effectiveness-the-qaly-and-the-evlyg/>. Published 2023. Accessed April 12, 2023.

¹⁷ Basu A, Carlson J, Veenstra D. Health Years in Total: A New Health Objective Function for Cost-Effectiveness Analysis. *Value Health.* 2020;23(1):96-103.

¹⁸ Lakdawalla DN, Phelps CE. Health technology assessment with risk aversion in health. *J Health Econ.* 2020;72:102346.

¹⁹ Cohen JT, Neumann PJ, Ollendorf DA. The much-maligned ‘quality-adjusted life year’ is a vital tool for health care policy [Opinion]. *Stat.* 2023. <https://www.statnews.com/2023/03/22/the-much-maligned-quality-adjusted-life-year-is-a-vital-tool-for-health-care-policy/>. Published March 22. Accessed April 14, 2023.

²⁰ Shafrin J LD, Doshi JA, et al. A Strategy for Value-Based Drug Pricing Under the Inflation Reduction Act. In: Affairs H, ed. *Health Affairs Forefront.* Forthcoming.

²¹ Sullivan SD LD, Devine B. Alternatives to the QALY for Comparative Effectiveness Research. In: Affairs H, ed. *Health Affairs Forefront.* Forthcoming.

²² Phelps CE, Lakdawalla DN, Basu A, Drummond MF, Towse A, Danzon PM. Approaches to Aggregation and Decision Making-A Health Economics Approach: An ISPOR Special Task Force Report [5]. *Value Health.* 2018;21(2):146-154.

issued a pair of Task Force reports^{23,24} that describe how MCDA works. In this case it would involve having a group of educated stakeholders weigh relevant measures, including a clinical benefit measure but not necessarily the QALY, in a process that results in a single value measurement. MCDA can be conducted in a way that uses different value elements in different cases but can be comparable across cases as long as a common clinical benefit measure is employed.

Second, the broader qualitative process CMS intends to use can be informed by, or could directly use, a deliberative process as well, which has been described for use in health technology assessment (HTA).²⁵ Deliberative processes for HTA are intended to facilitate participatory decision making, using discussion and open dialogue between stakeholders. They are a specific instance of the type of process that employs “accountability for reasonableness”²⁶ as a basis for establishing fairness. We encourage CMS to consider such an approach.

6. **General process considerations.** This initial year involves some relatively short timelines that are necessary due to the legislation and do not realistically offer time for deliberative processes and may limit meaningful stakeholder engagement. We encourage CMS to consider extending timelines for future years to facilitate transparency in these assessment methods (preferably including a memorandum detailing the qualitative process that becomes used) and allow for more extensive engagement and deliberation. We also encourage CMS to consider adapting their guidance for this process based on learnings from the initial implementation experience.

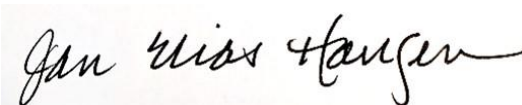
We thank CMS for the opportunity to comment on this consultation; if you have questions about any of these comments, please contact our Chief Science Officer, Richard Willke, at rwillke@ispor.org.

We look forward to working with CMS throughout the implementation of the program. We know this will be a multiyear process and that approaches and methods may change along the way. We welcome the opportunity for further discussion about the considerations in this response and to engage in additional consultations.

Sincerely,



Robert Abbott
CEO & Executive Director
ISPOR



Jan Elias Hansen, PhD
President 2022-2023, ISPOR
Vice President, Evidence for Access, Genentech

²³ Marsh K, IJzerman M, Thokala P, et al. Multiple Criteria Decision Analysis for Health Care Decision Making--Emerging Good Practices: Report 2 of the ISPOR MCDA Emerging Good Practices Task Force. *Value Health*. 2016;19(2):125-137.

²⁴ Thokala P, Devlin N, Marsh K, et al. Multiple Criteria Decision Analysis for Health Care Decision Making--An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force. *Value Health*. 2016;19(1):1-13.

²⁵ Oortwijn W, Husereau D, Abelson J, et al. Designing and Implementing Deliberative Processes for Health Technology Assessment: A Good Practices Report of a Joint HTAI/ISPOR Task Force. *Value Health*. 2022;25(6):869-886.

²⁶ Daniels N. Accountability for reasonableness. *BMJ*. 2000;321(7272):1300-1301.

APPENDIX: ISPOR Task Force and other Reports Referenced in this Document (numbered as listed in the letter footnotes)

3. 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. <https://doi.org/10.1111/j.1524-4733.2009.00600.x>
4. 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—part II. *Value Health*. 2009;12(8):1053-1061. <https://doi.org/10.1111/j.1524-4733.2009.00601.x>
5. 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. <https://doi.org/10.1111/j.1524-4733.2009.00602.x>
6. 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 <https://doi.org/10.1002/pds.4297>
7. 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. <https://doi.org/10.1002/pds.4295>
8. 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. <https://doi.org/10.1016/j.jval.2013.12.011>
9. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health*. 2011;14(4):417-428. <https://doi.org/10.1016/j.jval.2011.04.002>
10. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value Health*. 2011;14(4):429-437. <https://doi.org/10.1016/j.jval.2011.01.011>
11. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-

NPC Good Practice Task Force report. Value Health. 2014;17(2):157-173.

<https://doi.org/10.1016/j.jval.2014.01.004>.

12. Lakdawalla DN, Doshi JA, Garrison LP, Jr., 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. <https://doi.org/10.1016/j.jval.2014.01.004>.

14. 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.

<https://doi.org/10.1016/j.jval.2022.01.010>

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