Society for Women's Health Research

October 18, 2019

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, MSc, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: ICER Proposed Changes to its 2020 Value Assessment Framework

Dear Dr. Pearson:

The Society for Women's Health Research (SWHR) appreciates the opportunity to provide public comment on proposed changes to the Institute for Clinical and Economic Review (ICER) 2020 value assessment framework. SWHR is a nearly 30-year-old education and advocacy nonprofit dedicated to promoting research on biological sex differences and improving women's health through science, policy, and education. We are uniquely positioned to serve as a resource to ICER on key aspects of value assessment that have implications for women and their health.

SWHR's open input comments from June 10 offered practical information and suggestions on how ICER can improve the methods it uses to assess the value of drugs and health care interventions and the processes it follows to engage with stakeholders. On October 11, we shared with ICER a set of principles that SWHR conceived to help ensure that value frameworks and assessments, including those of ICER, reflect factors relevant to women and the ongoing improvement of their health, as well as allow for access to new therapies.

While we are encouraged that ICER's proposed updates released on August 21 provide some incremental improvements that align with SWHR principles, the changes do not go far enough to support optimal health outcomes for women as patients, caregivers, and health care decision-makers for themselves and their families. As previously stated

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in our June 10 open input letter and in SWHR's Health Care Value Assessment Principles, women's roles in health care are complex and multifaceted. Therefore, the framework should be designed to incorporate specific challenges faced by individuals interacting with the health care system from a variety of perspectives.

- Women comprise more than half (51%) of the U.S. population.[1]
- Women provide the majority of caregiving.
  - Nearly 70% of caregivers are female.[2]
  - Women assume multiple roles while caregiving: hands-on caregiver, case manager, companion, decision-maker, and advocate.
- Women make more than 80% of health care spending decisions.[3]

SWHR appreciates this opportunity to provide recommendations and feedback in response to ICER's proposed value framework.

Section 1.2 (Population Perspective and Intended Uses)

SWHR Recommendation 1: Consider and account for population differences (including sex and gender) to inform what is or is not known about the variation in response to different treatments.

ICER states that one important goal of its value framework is "*to provide an evidence report that does a better job of analyzing the strengths and limitations of the available evidence, including what is or is not known about the variation in response to different treatments among patients with different personal and clinical characteristics*" [lines 368-371].

As discussed in SWHR's June 10 comments, *sex* and *gender* play critical roles in the risk, pathophysiology, presentation, diagnosis, treatment, and management of disease.

- *Sex* refers to the classification of living things according to reproductive organs and functions assigned by chromosomal complement.[4]
- *Gender* refers to the social, cultural, and environmental influences on the biological factors of women or men. Gender is rooted in biology and shaped by environment and experience.[5]

The increased study of sex and gender differences is leading to important discoveries of how women and men differ in fundamental ways and how these differences affect disease risk, symptoms, diagnostic sensitivity and specificity, and response to therapy. Biological and physiological differences and hormonal fluctuations have been shown to play a role in the rate of drug absorption, distribution, metabolism, and elimination, resulting in different drug responses in women and men.[6] ICER should consider and account for population differences including sex and gender in its value framework to inform what is or is not known about variation in response to different treatments.

Society for Women's Health Research

Section 3.1 (Sources of Evidence)

SWHR Recommendation 2a: Use a broad range of high-quality, real-world evidence sources.

SWHR is pleased that ICER reaffirmed its commitment to using existing real-world evidence (RWE) for future reviews. RWE is clinical evidence derived from analysis of real-world data (RWD) about the usage and potential benefits or risks of a medical product.[7]

As discussed in our June 10 comments, as the availability of RWE grows, all value assessment organizations, including ICER, should seek to increase the use of a broad range of high-quality RWE sources in its reviews.

Although RWE will not be available for new drugs at launch, it may be available for marketed products, making it potentially useful for therapeutic class reviews as well as updated reviews. Importantly, RWE may provide important information to assess whether outcomes differ by *sex and gender*.

SWHR Recommendation 2b: Articulate ICER principles and methods for incorporating RWE into future topic reviews, including discussion of when RWE may be discarded.

In Section 3.1, ICER states that *"as with all evidence, ICER will assess the internal and external validity of RWE as part of a larger judgment of whether and how that evidence should be incorporated in an assessment. As part of this broad commitment, ICER will continue to formally request that stakeholders who are engaging on a review project submit relevant RWE for consideration in the evidence review"* [lines 389-393].

As SWHR suggested in our June comments, ICER should articulate not only overarching principles but corresponding systematic methods for evaluating RWE in future topic reviews, including discussion of instances where ICER may discard RWE in favor of exclusive use of randomized clinical trials (RCTs). ICER should leverage existing resources, information, and best practices from experts in the field instead of initiating *de novo* work in this area. A few examples are:

- In December 2018, FDA released a detailed framework outlining how the agency will evaluate RWE intended to support approval of a new indication for an approved drug or biologic, or to help support or satisfy drug post-approval study requirements. This framework will serve as a roadmap for the inclusion of RWD and RWE in regulatory decisions, including standards on how RWD is defined, collected, and analyzed. FDA will also provide guidance on RWE study methodologies and designs that meet regulatory requirements in generating evidence of effectiveness, among other topics.

- In September 2019, the Duke-Margolis Center for Health Policy released Determining Real-World Data's Fitness for Use and the Role of Reliability, a new white paper that outlines a framework for how researchers and reviewers can systematically evaluate whether RWD are fit for use by using verification checks to assess reliability. This paper

aims to serve as a resource for sponsors in designing studies using RWD sources, for regulators in developing policy, and for researchers in developing study methodology best practices.

SWHR Recommendation 2c: Outline ICER process for generating and analyzing new RWE with potential collaborators.

In Section 3.1, ICER also states that it *"will seek opportunities to generate new RWE for incorporation in reviews. ICER will explore collaborative relationships with organizations that may serve as sources of real-world data in order to generate RWE during reviews that can complement published data sources"* [lines 395-397].

SWHR supports the concept of ICER working collaboratively with organizations that may serve as sources of RWD and/or have expertise in analyzing RWE that could be leveraged for new analyses. ICER provides limited details, however, regarding a) the process it will undertake to identify potential RWE partners and b) the methods it will use to make judgments about whether RWE analyses will *"address key gaps in the evidence base and be feasible within the timeframes of an ICER review"* [lines 423-424].

SWHR urges ICER to proceed thoughtfully in developing its vision, methods, and process for generating new RWE for use in its assessments. ICER's historical role has been to evaluate evidence, not generate it. Therefore, we ask that ICER clarify its own role, capability, and capacity to perform *de novo* RWD/RWE studies. We also encourage ICER to outline a well-articulated process for working with organizations to leverage their expertise in generating and analyzing RWE to develop and test best practices for determining when and how RWE should be incorporated into future topic reviews.

Section 3.3 (Cross-Reference with German Evidence Ratings)

SWHR Recommendation 3: Drop new proposal to cross-reference with German evidence ratings.

ICER introduces a new proposal to *"provide complementary evidence ratings using the German categories of 'added benefit'"* [lines 470-471]. In addition to its own evidence ratings, ICER *"will seek to translate its judgment of the evidence into the rating system for added clinical benefit used in Germany to summary drug assessments and guide pricing considerations"* [lines 471-473].

Interest and use of ICER's work in other pharmaceutical markets should not be a catalyst for ICER to translate evidence using its *"own judgment of 'added benefit' within the German categories to complement ICER's own methods"* [lines 485-486]. ICER's use of a *"rough algorithm for the crosswalk between the two systems"* [lines 516-517] that relies on ICER's own judgement is concerning because it is inconsistent with ICER's stated charter to objectively

evaluate the clinical and economic value of health care innovations.[8] SWHR recommends ICER reconsider this proposal and drop the cross-reference with German Evidence Ratings from its 2020 value assessment framework update.

Section 3.4 (Base-Case Perspective in Economic Models)

SWHR Recommendation 4: Include societal perspective as a base case in cost-effectiveness models.

While ICER currently conducts cost-effectiveness analyses (CEA) from both the health care sector and societal perspectives, it *"chooses to use the health system perspective as the basis for its primary base-case results"* [lines 857-859]. Excluding relevant costs outside of those incurred by the health care sector (i.e., insurance or a national payer) obscures critical cost savings that capture the comprehensive value of a new intervention/therapy.

SWHR urges ICER to include the societal perspective as an additional base case of CEA for future reviews to ensure that factors important to women such as productivity and caregiver burden are reflected in ICER value-based price benchmarking for a technology/therapy. Use of the societal perspective is an established health economics methodology that is recommended by the Second Panel on Cost-Effectiveness in Health and Medicine, a nonfederal panel with expertise in CEA, clinical medicine, ethics, and health outcomes measurement convened by the U.S. Public Health Service (PHS).[9] ICER should include societal base-case results in all of its reports and summaries (i.e., press results and report-at-a-glance documents).

Section 3.6. (Alternative Economic Model Assumptions)

SWHR Recommendation 5a: Increase subgroup analyses to capture patient heterogeneity.
SWHR Recommendation 5b: Incorporate subgroup value metrics to quantify treatment option optimization among patient populations more narrowly.

SWHR is encouraged that ICER will *"include scenarios with different patient subgroups to account for the heterogeneity within patient groups within a specific disease area"* [lines 1067-1068]. SWHR's June comments discussed the need for ICER methods to incorporate patient subgroup outcomes and treatment preferences into its value framework. As discussed in Section 1.2 (Population Perspective and Intended Uses), this is necessary to understand how patients may respond differently to therapy and health interventions based on factors such as sex and gender, age, genetic variation, stage of illness (e.g., severe vs. mild disease, advanced vs. early disease), and comorbidities (absence vs. presence). Value frameworks such as ICER's should capture patient heterogeneity and have the analytic capability to report more than a single value-based price for an average patient.

We urge ICER to explore opportunities for building subpopulation value metrics into its model, such as subpopulation cost-effectiveness ratios (e.g., male vs. female), which could present a way to account for treatment option optimization among patient populations more narrowly.

SWHR Recommendation 6: Quantitatively account for a broad array of patient and societal factors to reflect a treatment's value comprehensively.

Value assessment frameworks should account for what matters most to patients, caregivers, and society, in addition to measuring clinical outcomes. To provide a comprehensive snapshot of a treatment's value, a broad array of factors should be considered and quantitatively accounted for in value assessment cost-effective methodologies.

As outlined in SWHR Health Care Value Assessment Principle #3 and our June comments, burden of illness factors that are important to women include (but are not limited to):

- Survival
- Ability to function/work
    - Presenteeism
    - Absenteeism
    - Employment disability
- Quality of life
    - Physical and social well-being
    - Pain or discomfort
- Levels of disease burden and progression
- Comorbid conditions or concomitant medications
- Caregiver burden[10]
    - Permanent difficulty, stress, or negative experiences resulting from providing care[11]
    - Physical, emotional, and financial cost of the caregiving
- Limitations in treatment
    - None (i.e., a treatment does not exist for a particular condition or disease)
    - Limited options (i.e., there have been few innovations in the disease state, the products on the market are contraindicated for a subset or subsets of patients, or available therapy does not meet the patient's preference).

Despite ICER receiving comments from SWHR and many others on this issue, ICER continues to hold firm and leave the consideration of these important factors up to the discretion of the voting panel. Consequently, the impact of these factors is not being systematically measured. SWHR urges ICER to partner with qualified research organizations to develop, test, and pilot a methodology to integrate these factors into ICER value assessments in a transparent manner to allow for and maximize stakeholder input and collaboration.

Society for Women's Health Research

Section 6.1 (Report Development)

SWHR Recommendation 7: Align timing of value assessments with availability of pertinent data.

ICER often conducts its reviews before complete data are available. In some instances, ICER has determined cost-effectiveness of a therapy ahead of its market introduction and public announcement of its price. For example:

- In its draft evidence report on endometriosis, ICER repeatedly acknowledged important limitations both in the available evidence and in its own analysis, which calls into question the timing of the value assessment and the validity of its conclusions.[12]

- In its final evidence report on endometriosis, the New England Comparative Effectiveness Public Advisory Council (CEPAC) *"did not deliberate or vote on the value of elagolix because the manufacturer had not yet announced the launch price, and ICER's economic evaluation had therefore used a placeholder price."*[13]

SWHR urges ICER to trigger the timing of its topic reviews when pertinent data (clinical trial, accurate pricing, and real-world evidence) are available.

SWHR Recommendation 8: Further extend stakeholder review times.

Value assessment organizations, including ICER, should provide ample opportunities for stakeholder engagement to ensure their input is both acknowledged and meaningfully incorporated into assessments. This includes allowing sufficient time for stakeholders to review materials and submit comments in various stages throughout the assessment process.

SWHR appreciates that ICER acknowledged this recommendation in its updated framework and proposes to extend the review time for large-class reviews by nine weeks. Extending the draft report public comment period by one week represents a modest improvement but remains inconsistent with established and customary timeframes for other stakeholder review timeframes. As discussed in SWHR Health Care Value Assessment Principle #6, federal government public comment periods typically are not less than 30 days and frequently are a minimum of 60 days.

We ask ICER to further extend stakeholder review times to be consistent with those of the federal government and other health technology assessment organizations (e.g., not shorter than 60 days).

SWHR Recommendation 9: Update assessments to account for new innovation and changes to the evidence base as needed.

SWHR agrees with ICER that *"stakeholders would benefit from a formal process to indicate whether report findings remain applicable or that new developments have occurred that could lead to different conclusions"* [lines 1424-1426].

Incorporating longer-term outcomes is important to account for the full value of a therapy or intervention, particularly as additional evidence continues to emerge post-approval. In addition, patient perceptions of value change over time as their individual circumstances and experience of illness and treatment evolve through the course of disease (i.e., shifts in prognosis, severity of illness, comorbidities, available treatment/palliative options, and life events such as pregnancy or menopause). (See SWHR Health Care Value Assessment Principle #3.)

SWHR supports ICER's proposal to implement a review process, to be completed around the one-year anniversary of a final report that will summarize in a public statement ICER's rationale for why it will or will not update the assessment. We encourage ICER to outline a well-articulated process and timeline for how it will conduct assessment updates to final reports.

SWHR Recommendation 10: Include additional information on patient perspectives.

ICER proposes to create a new chapter on patient perspectives that will follow the background chapter in its assessment reports. SWHR supports inclusion of patient-centered information in the early pages of each assessment. Such information is important for all audiences, particularly members of the voting panel, who need to have a more comprehensive understanding of the patient experience and the burden of varying illness factors. As a next step, ICER should outline its proposed process for soliciting input from stakeholders, as well as the criteria it will use to decide what patient perspective information will or will not be included in this new chapter for all future assessment reports.

Section 6.2 (Public Meetings)

SWHR Recommendation 11: Include disease experts on ICER voting councils.

ICER's council membership by design does not necessarily include those affected by the condition under review. Seeking input from patient and clinical experts throughout the report development process does not compensate for this lack of critical representation.

Stakeholders who have direct experience and expertise with a particular illness and its burden should be appropriately represented on ICER's voting councils that make determinations about a treatment's value. As outlined in SWHR Health Care Value Assessment Principle #6, we strongly urge ICER to reconsider the design and composition of its council membership and voting councils to include representation from the following stakeholders in each of its assessments:

- Patients who are diagnosed with the disease/condition under review;
- Health care professionals who actively treat patients with the disease/condition under review; and
- Caregivers who assist patients with care needs for the disease/condition under review.

Society for Women's Health Research

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Thank you for the opportunity to provide these comments and for ICER's thoughtful consideration of our proposals. We look forward to serving as a resource on this and other topics affecting women's health. If you have questions, or if we can provide further information to inform ICER's update to its value assessment framework, please contact Sarah Wells Kocsis, Vice President of Public Policy, at 202.496.5003 or swellskocsis@swhr.org.

Sincerely,

Amy Miller, PhD
President and Chief Executive Officer
Society for Women's Health Research

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