Society for Women's Health Research

June 10, 2019

Submitted electronically to: publiccomments@icer-review.org

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Dear Dr. Pearson:

The Society for Women's Health Research (SWHR) appreciates the opportunity to provide input to the Institute for Clinical and Economic Review (ICER) on the 2020 update to its value assessment framework. SWHR, an education and advocacy thought leader, is dedicated to promoting research on biological differences in disease and improving women's health through science, policy, and education.

SWHR is committed to ensuring value frameworks are appropriately designed and used to inform decision-making to achieve optimal health outcomes for women as patients, caregivers, and health care decision-makers for themselves and their families.

- 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 is pleased to offer these comments and suggestions on how ICER can improve the methods it uses to work with stakeholders and to assess the value of drugs and health care interventions.

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1. *Account for diversity in patient populations and subgroups (including sex and gender).*

Sex and *gender* play critical roles in the risk, pathophysiology, presentation, diagnosis, treatment, and management of disease. As defined by the Institute of Medicine:

- *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]

When women are underrepresented in clinical trials, outcomes from predominantly male cohorts have driven clinical guidelines that are not sex specific.[6] 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.[7]

ICER's value assessment framework should account for diversity in patients (including sex and gender) for a given disease state by analyzing data that represents relevant patient populations and subgroups.

2. *Explore subpopulation value metrics.*

ICER's framework takes a population-level perspective versus a shared decision-making tool approach for use by patients and their clinicians, and ICER acknowledges the limitations of representing patient diversity with a population-level focus:

> *"Representing the diversity of patient outcomes and values in a population-level framework is difficult because there will always be an inherent tension between the average findings in clinical studies and the uniqueness of every patient."*[8]

Given these limitations, ICER should improve upon its methodologies to incorporate patient subgroup outcomes and preferences for treatment into its value framework. As discussed above, examining patient subgroups is imperative to understanding 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.

3. Ascertain whether clinical trial data are representative of the relevant patient population.

ICER's current value framework relies heavily on clinical trial data for its evaluations. Predominant reliance on clinical data can underrepresent certain patient populations and subgroups, such as women and people of racial and ethnic minority groups.

ICER should incorporate methods to evaluate whether the clinical trial data used in a given value assessment are representative of the relevant patient population and subgroups. SWHR encourages ICER to review publicly available data sources to inform this determination. For example, the Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA) posts online Drug Trial Snapshots that show who participated in pivotal clinical trials used to approve a novel drug that is either a new molecular entity or original biologic product. The Snapshots stratify the clinical trial data by sex, race, age, and ethnicity groups, and also provide statements on observed differences in safety and efficacy by demographic subgroups at the time of approval. CDER has published a Snapshot for each novel drug approved within one month of the official FDA approval date since January 2015.

Drug Trial Snapshots for three FDA-approved drugs for migraine report that 85% or greater of the participants enrolled in FDA clinical trials to evaluate safety were women.[9] This percentage is consistent with the population affected by the condition, which affects women differently than men,[10] and shows that women were represented as a population subgroup in the clinical trial data.

4. Quantify factors that matter to patients and society and integrate them into ICER value assessments.

ICER's Patient Guide to Open Input for its 2020 value framework update states that "it is critically important that the patient perspective be fully captured in [its] work."[11] SWHR strongly agrees that any value assessment should aim to understand the diversity of the patient experience. Examples of burden of illness factors that are important to women include (but are not limited to):

- Survival
- Ability to work
  - Presenteeism
  - Absenteeism
  - Employment disability
- Quality of life
  - Physical and social well-being
  - Pain or discomfort
- Levels of disease burden and progression
- Comorbid conditions
- Caregiver burden[12]

    - Permanent difficulty, stress, or negative experiences resulting from providing care[13]
    - Physical, emotional, and financial cost of the caregiving
- Limitations in treatment
    - None
    - Limited options

ICER's current approach deems factors like these as "additional benefits/contextual considerations" and does not formally incorporate them into its assessment results. By leaving them up to the discretion of the voting panel, their impact is not being systematically measured. To provide a comprehensive picture of a treatment's value, ICER's value assessments should quantitatively account for a broad array of factors that are important to patients and society, such as those listed above.

5. Use a broad range of high-quality, real-world evidence sources.

Patients have characteristics and treatment experiences that often differ from the controlled environment of clinical studies. Data on caregivers — the majority of whom are women — have not been routinely collected in clinical trials. That is why understanding how treatments work in real-world clinical settings — with input from patients and caregivers — is so important.

Real-world evidence is derived from data collected during routine health care practice (such as electronic health records, claims and billing activities, or product and disease registries) and is often collected *after* a new therapy is already on the market and being used by patients. 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.

SWHR is pleased that ICER has stated its intent to explore ways to incorporate RWE into its work. While RWE will not be available for new drugs at launch, it may be available for marketed products and can be useful for therapeutic class reviews and updated reviews by providing critical information to assess whether outcomes are different by sex and gender.

As part of its 2020 framework update, ICER should outline its process and systematic approach for increased use of RWE in future topic reviews. ICER's approach should review recent and current RWE initiatives and seek to leverage existing resources, information, and best practices, instead of initiating de novo work in this area. Some examples include:

- 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 real-world data (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.

- On July 11 and 12, 2019, the Robert J. Margolis, MD, Center for Health Policy at Duke University will convene a public stakeholder workshop to examine considerations for using randomized designs to generate RWE. The public workshop is a part of ongoing efforts to explore the utility of RWE and inform FDA's strategic framework.
- In July 2017, National Health Council convened a daylong, multi-stakeholder roundtable to gather patient community views on RWE and related concerns as well as the communications, information, and tools needed by patients to understand, trust, and use RWE. A published report followed outlining 10 themes that emerged from the discussion.[14]

6. Leverage existing approaches for systematically capturing patient and caregiver input.

Generating high-quality patient data that addresses patient needs is of great interest and priority to diverse stakeholders throughout the U.S. health care system. Recent legislation — the 21st Century Cures Act and sixth authorization of the Prescription Drug User Fee Act (PDUFA VI) — gave FDA significant new directives to address patient needs as part of advancing medical innovation. FDA's Patient Focused-Drug Development (PFDD) Program is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation by:

- facilitating and advancing systematic approaches for collection and use of robust and meaningful patient and caregiver input to more consistently inform drug development and regulatory decision-making;
- encouraging identification and use of approaches and best practices to facilitate patient enrollment and minimize the burden of patient participation in clinical trials;
- enhancing understanding and appropriate use of methods to capture information on patient preferences and the potential acceptability of tradeoffs between treatment benefit and risk outcomes; and
- identifying information that is most important to patients related to treatment benefits, risks, and burden, and how to best communicate the information to support their decision-making.

SWHR encourages ICER to review patient experience data sources and methods outlined in FDA draft guidance (and public comments in response to them) to inform how this initiative and significant work to date could be leveraged and incorporated in ICER's value assessment framework.

In May, the National Alliance for Caregiving, in partnership with the LEAD Coalition, published Paving the Path for Family-Centered Design: A National Report on Family Caregiver Roles in Medical Product Development. The report highlights where caregiver insights might be most useful at each stage of medical product research and development and presents recommendations

for leveraging the existing policy and emerging practices to tap the wisdom of caregivers about the conditions their care recipients experience and the health care outcomes that matter most. SWHR encourages ICER to draw upon "Paving the Path" report findings and recommendations to identify ways to better integrate caregivers and their perspectives into ICER's value assessment framework.

7. Develop standards for using patient experience data in value frameworks.

SWHR strongly supports the development of consensus-driven standards for patient data collection, submission, and management. To be reliable and effective, such standards must be based on methodologically sound approaches that accommodate the distinct and varying perspectives of patients on the value of interventions, while simultaneously collecting patient experience data that is relevant, objective, accurate, and representative of the target patient population. Standards should be flexible, with the capacity to evolve over time. As stakeholders gain more experience with data collection, submission, and management, standards and processes may need to be revisited and revised.

SWHR encourages ICER to facilitate constructive dialogue with key stakeholders including industry, patient advocacy organizations, and federal agencies to allow for a transparent and organized process for developing standards for the collection, submission, and management of patient experience data used in value assessments.

8. Elaborate on ICER's use of cost-effectiveness analysis (CEA) registry data in value assessments.

A January 15, 2019, press release issued by the Tufts Center for the Evaluation of Value and Risk in Health (CEVR) announced that ICER had begun using the CEVR cost-effectiveness analysis (CEA) registry — a comprehensive database of 7,287 cost-utility analyses on a wide variety of diseases and treatments published from 1976 to 2017 — to help evaluate drugs and other medical interventions.

ICER has provided limited details about how it is using the CEVR CEA registry in its topic reviews. SWHR could not find any mention of the CEVR CEA registry on ICER's website. As part of its update to the 2020 value assessment framework ICER should discuss in a transparent manner how it is using the CEVR CEA registry in topic reviews.

9. 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, ICER conducted its assessment of cholesterol-lowering PCSK9 inhibitors before clinical trials were completed. In its draft evidence report on endometriosis, ICER repeatedly acknowledged important limitations both in the available evidence and in its own analysis, calling into question the timing of the value assessment and the validity of its conclusions. Missing or incomplete data lead to a flawed valuation. SWHR urges

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

10. Extend stakeholder review times.

Value assessment organizations should provide ample opportunities for stakeholder engagement to ensure their input is both acknowledged and meaningfully incorporated into assessments. ICER should announce proposed assessment topics, processes, and timelines in advance to allow for participation by stakeholders, especially those with limited resources. ICER should also allocate sufficient time for stakeholders to review materials and submit comments in various stages throughout the assessment process. Assessments should be regularly updated to account for new innovation and other changes in the evidence base.

SWHR appreciates that ICER "adheres to tight timelines for each report in order to balance timing of expected drug approvals with decision-makers' need for timely information to inform policy and practice."[15] While we understand that comment periods need "to be limited to ensure ICER staff to review comments and incorporate them into reports,"[16] we urge ICER to further reflect on the numerous comments expressing concern with the timeline for public comment submissions. Three weeks is not sufficient time for stakeholders — particularly small, under-resourced ones — to respond. Extending the timeline even by a few weeks would be helpful for stakeholders to engage and provide meaningful review and feedback.

11. Foster greater transparency of value assessment, processes, methodologies, and results.

Explanation of value assessment criteria, methodologies, and assumptions should be understandable to patients and other stakeholders. Models and data should be publicly available to allow others to analyze the research and replicate results.

SWHR commends ICER for its commitment to a transparent public engagement process to ensure that all stakeholders have the opportunity to provide input to its reports and updates to its value assessment framework. We were pleased that ICER took steps last year to make draft executable economic models available to manufacturers during the assessment review process. While we agree with ICER that enabling the direct viewing of a model's structure, estimates, key assumptions, and calculations may allow for valuable feedback during the public comment period that follows the release of an ICER draft evidence review, ICER's current approach has limitations. Access to the models remains too restrictive. ICER should make models available to qualified researchers, not just for review but for customization and reproducibility, and it should relax confidentiality agreements to foster greater discussion among interested parties.

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Thank you for considering the above input. 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

Society for Women's Health Research

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Sincerely,

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

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