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May 31, 2018

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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

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 a range of chronic, debilitating, painful conditions disproportionately or exclusively affecting women.

SWHR, a nonprofit organization based in Washington, DC, is widely recognized as a thought leader in promoting research on biological differences in disease and eliminating imbalances in care for women through science, policy, and education.

SWHR appreciated the opportunity to submit an open input letter on endometriosis to ICER on February 1, 2018, and we continue to follow closely the methodology ICER is employing to assess the effectiveness and value of new therapies for endometriosis, including the GnRH antagonist, elagolix. Because endometriosis exclusively affects women, any value assessment of new therapies must take a female-centered approach that reflects the condition's unique patient experience, disease burden, and impact to society.

SWHR urges ICER to delay finalizing the Draft Evidence Report (DER) until new therapies, such as elagolix, are FDA-approved and more published data is available to model the comparative clinical and economic value of new treatment options for endometriosis. If ICER insists on moving forward with this DER, we strongly encourage ICER to take immediate steps to strengthen its analysis by making needed refinements to its methodology, modeling techniques, and key inputs.

The Burden of Endometriosis on Women

Endometriosis affects approximately 10% of reproductive-age women.¹ Its cause remains unknown and there is no cure. It is estimated that more than 200 million women and teens worldwide have been diagnosed with endometriosis^{2,3} and about 71% to 87% of these women and girls experience pelvic pain.^{4,5,6} The serious emotional, physical, and financial burdens associated with endometriosis affect not only women living with the disease, but their families and society as a whole.

- **Nearly all women with endometriosis report having one or more comorbid disorders.**⁷ Common comorbidities include migraine, depression, anxiety, upper respiratory infections, uterine fibroids, and ovarian cysts.^{8,9,10} In addition, endometriosis is associated with risk for some chronic diseases, such as several types of cancer, autoimmune diseases, asthma, and cardiovascular disease.¹¹
- **It can take years for a woman to receive an endometriosis diagnosis.** On average, women with endometriosis make seven healthcare professional visits before being referred to specialists, with an average diagnostic delay of 6.7 years,¹² and nearly three-quarters have had a misdiagnosis.¹³ Reasons for delays in the diagnosis of endometriosis include stigma; attitudes toward menstruation and the “normalization” of pain; nondiscriminatory exams (both digital examination and transvaginal ultrasound); intermittent use of contraception causing hormonal suppression; and misdiagnosis.
- **Women suffering from endometriosis may experience stigma.** Although endometriosis is one of the most common gynecological conditions, there is lack of public awareness and understanding of the disease, a societal normalization of women’s pain, and too few available treatment options. The resulting stigma can prevent women suffering from endometriosis from seeking and receiving appropriate care, treatment, and compassion.
- **Total healthcare costs, *even prior to diagnosis*, are significantly higher for women with endometriosis compared to those without endometriosis.**¹⁴ Even five years pre- and post-diagnosis, total healthcare costs (medical and prescription) were significantly higher for women with endometriosis.¹⁵ During this same time period, a significantly higher proportion of women with endometriosis had outpatient and emergency room visits compared to women without endometriosis. Additionally, in the year prior to diagnosis and five years post-diagnosis, the length of an inpatient hospital stay was significantly longer for women with endometriosis compared to those without the disease. These findings demonstrate the critical need for innovations in endometriosis and the importance for women to have access to them.
- **The societal cost of endometriosis is staggering.** In the United States, the economic burden of endometriosis (direct and indirect costs) is estimated to be \$69.4 billion.^{16,17}

Key Issues and Recommendations on ICER Endometriosis DER

SWHR agrees with ICER that there is an important unmet need to treat patients with symptomatic endometriosis. With no cure or innovations for the past two decades, new diagnostic and therapeutic options have the potential to improve a woman's health status significantly and thus reduce the social and economic burdens associated with this disease, including medical expenses.

However, after reviewing the DER, SWHR is concerned that the current timing of ICER's value assessment of elagolix may be premature. Throughout the DER, ICER repeatedly acknowledges important limitations both in the available evidence and in its own analysis that call into question the timing of this value assessment and the validity of the conclusions. The following quotes demonstrate the multiple limitations of ICER's endometriosis DER analysis:

- Page 43: *“Importantly, we note that, due to differences in trial design, outcome measurement, the age of comparator studies, and other factors as highlighted in Section 3, our only recourse was to model the cost-effectiveness of elagolix as compared to no active treatment (i.e., placebo).”*
- Page 57: *“We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments. We found no published economic evaluations of elagolix in women with moderate-to-severe endometriosis related pain.”*
- Page 59: *“We note, however, that the only comparison available because of data limitations was to no active medical management (i.e., placebo), which is an unrealistic clinical strategy in women with moderate-to-severe endometriosis-associated pain.”*
- Page 59: *“There were several important and distinctive limitations to our analysis. ... severe limitations in available data precluded any comparison to another active treatment such as GnRH agonists and oral contraceptives. It is therefore likely that clinical benefits in our analysis are overstated to some extent, although the magnitude of this effect is unknown without comparable data. We also modeled cost-effectiveness using an assumed annual price, as the drug is not yet FDA-approved and the actual price is unknown.”*

Therefore, as we stated at the outset, SWHR urges ICER to delay finalizing the DER until new therapies, such as elagolix, are FDA-approved and more published data is available to model the comparative clinical and economic value of new treatment options for endometriosis. If ICER insists on moving forward with this DER, we strongly encourage ICER to take immediate steps to strengthen its analysis by making needed refinements to its methodology, modeling techniques, and key inputs. SWHR offers the following comments and recommendations for ICER's consideration:

- 1) ***ICER should account for lost productivity in the cost-effectiveness base case, instead of using lost productivity to estimate cost-outcomes from a modified societal perspective as a scenario analysis. Further, ICER's data capture of lost productivity must account for both presenteeism and absenteeism.***

Characterized by pain symptoms, endometriosis has a negative effect on productivity. Women with endometriosis suffered a 38% loss of work and productivity because of the symptoms.¹⁸ Total productivity loss in employed women with endometriosis averages 6.3 hours per week, with the majority of that loss due to presenteeism.¹⁹ Endometriosis also severely affects household productivity, with an average of 4.9 hours per week lost. Both lost work and household productivity can vary as a function of symptom severity, with patients who experience moderate to severe symptoms reporting the highest lost productivity.²⁰

On average, 6.6 days per annum are lost because of absenteeism and 31.8 days per annum are unproductive days at work, resulting in a total loss (absenteeism and presenteeism) of about \$10,178 per year. Applying the most commonly reported prevalence of endometriosis (10%) to the number of the employed U.S. female population aged 18-49 in 2014 (44,614,000), the total loss (absenteeism and presenteeism) would be about \$45.4 billion annually.²¹

- 2) ***Endometriosis quality of life data used in ICER's analysis may not adequately capture the disproportionate effect this disease has on women, their families, and society as a whole.***

Endometriosis greatly affects the quality of life for women, including their relationships and their ability to perform. Endometriosis often negatively impacts sexual relations, productivity in the workplace and at home, appetite, exercise, emotional well-being, sleep, and relationships.²² The Endometriosis Health Profile-30 questionnaire (EHP-30) and its shortened version (EHP-5) are the only endometriosis-specific tools for collecting patient-reported outcomes on quality of life that were designed with input from patients.²³ While these tools capture the physical, emotional, and social impact of endometriosis on the patient, they do not adequately capture the burden of endometriosis on the family. In addition, the EHP-30 has not been widely adopted into clinical practice.²⁴

- 3) ***ICER should not rely solely on the wholesale acquisition cost (WAC) of a drug (whose actual price is not yet known) to estimate a new treatment's budget impact.***

ICER relies on the wholesale acquisition cost of a drug to estimate the budget impact of a new treatment (and therefore the estimated number of patients who can access the treatment). Not taking into account the rebates and discounts frequently negotiated between payers and pharmaceutical manufacturers is likely to lead to inaccurate budget impact estimations. Similarly, basing the DER on a placeholder WAC estimate is likely to result in incorrect estimates of the value of new treatments. If payers rely on flawed estimates, it could have significant implications for women's access to important treatments for endometriosis. We encourage ICER to consider accounting for likely rebates and discounts in its estimates.

- 4) ***ICER should develop novel approaches to assessing value.***

Cost-effectiveness analysis (CEA) based on quality-adjusted life years (QALY) may not adequately capture the differences in preferences and clinical characteristics of women with

endometriosis. While we recognize that ICER has committed to using CEA as the basis for its value framework, many stakeholders have acknowledged the limitations of QALY-based CEA, particularly in accounting for heterogeneity.^{25,26} Women with endometriosis vary in age, employment, caregiver status, and socioeconomic status. A simple cost-effectiveness ratio cannot capture those differences. If the QALY is used (despite the limitations noted above), it should be recognized that no single threshold can or should be universally applicable, as thresholds are likely to vary by decision-maker, population, and disease.

5) ***ICER should refine its new transparency pilot program before expanding its use beyond migraine prevention and endometriosis reviews.***


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. We are encouraged by a new pilot program ICER recently announced to make available draft executable economic models during the assessment review process, which represents an important next step in ICER's stakeholder engagement efforts.

SWHR agrees 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 DER. Consistent with ICER's intended goal to "provide the opportunity for manufacturers, and ultimately patient groups and other qualified stakeholders to gain even greater insights into draft models so that their feedback can enhance the accuracy and relevance of final versions,"²⁷ ***we urge ICER to: 1) expand model access beyond manufacturers to qualified researchers, 2) eliminate financial barriers to access by waiving payable fees to ICER's academic collaborators, and 3) share models that qualified researchers can alter for their own analytic purposes.***

Thank you for your consideration of the above comments and recommendations. 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 value assessment, please contact Sarah Wells Kocsis, Vice President of Public Policy, at 202.496.5003 or swellskocsis@swhr.org.

Sincerely,



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

- ¹ Fourquet et al. *Fertil Steril*. 2011;96(1):107-112.
- ² Soliman et al. *Adv Ther*. 2018 Mar;35(3):408-423. doi: 10.1007/s12325-018-0667-3. Epub 2018.
- ³ Adamson et al. *J Endometr*. 2010;2(1):3-6.
- ⁴ Carter JE. *J Am Assoc Gynecol Laparosc*. 1994;2:43-47. (Level III)
- ⁵ Koninckx et al. *Fertil Steril*. 1991;55:759-765. (Level III)
- ⁶ Ling FW. *Obstet Gynecol*. 1999;93:51-58. (Level I)
- ⁷ Klein et al. *Reprod Biomed Online*. 2014 Jan;28(1):116-124. doi: 10.1016/j.rbmo.2013.09.020. Epub 2013 Sep 27.
- ⁸ Ibid.
- ⁹ Fuldeore et al. *Fertil Steril*. 2015 Jan;103(1):163-171. doi: 10.1016/j.fertnstert.2014.10.011. Epub 2014 Nov 15.
- ¹⁰ Cavaggioni et al. *BioMed Research International*. Vol 2014, Article ID 786830, <http://dx.doi.org/10.1155/2014/786830>
- ¹¹ Kvaskoff et al. *Hum Reprod Update*. 2015;21(4):500-516.
- ¹² Nnoahahm et al. *Fertil Steril*. 2011 Aug;96(2):366-373.e8. doi: 10.1016/j.fertnstert.2011.05.090.
- ¹³ Hudelist et al. *Hum Reprod*. 2012 Dec;27(12):3412-3416. doi: 10.1093/humrep/des316.
- ¹⁴ Fuldeore et al. *Fertil Steril*. 2015 Jan;103(1):163-171. doi: 10.1016/j.fertnstert.2014.10.011. Epub 2014 Nov 15.
- ¹⁵ Ibid.
- ¹⁶ Simoens et al. *Hum Reprod*. 2012;27:1292-1299.
- ¹⁷ Soliman et al. *Adv Ther*. 2018 Mar;35(3):408-423. doi: 10.1007/s12325-018-0667-3. Epub 2018.
- ¹⁸ Nnoahahm et al. *Fertil Steril*. 2011 Aug;96(2):366-373.e8. doi: 10.1016/j.fertnstert.2011.05.090.
- ¹⁹ Soliman et al. *JManag Care Spec.Pharm*. 2017;23(7):745-754.
- ²⁰ Ibid.
- ²¹ Ibid.
- ²² Fourquet et al. *Fertil Steril*. 2010;93(7):2424-2428. doi: 10.1016/j.fertnstert.2009.09.017.
- ²³ Khong et al. *Fertil Steril*. 2010 Oct;94(5):1928-1932. doi: 10.1016/j.fertnstert.2010.01.047. Epub 2010 Mar 2.
- ²⁴ Ibid.
- ²⁵ Lavelle et al. *Medical Decision Making*. 2018;38(4):487-494. <http://journals.sagepub.com/doi/abs/10.1177/0272989X17746989>
- ²⁶ PIPC White Paper: Uses and Misuses of the QALY-Ethical Issues and Alternative Measures of Value. June 21, 2017. <http://www.pipcpatients.org/resources/white-paper-uses-and-misuses-of-the-qaly-ethical-issues-and-alternative-measures-of-value>
- ²⁷ ICER Press Release March 30, 2018.