Response to ICER's Draft Scoping Document Regarding Elagolix for Endometriosis

AbbVie appreciates the opportunity to provide comments on the draft scoping document on elagolix for endometriosis, and respectfully recommends the following items be taken into consideration when finalizing the scoping document.

Target Population: *AbbVie agrees with ICER that there is an unmet need and 'considerable interest in new therapeutic options to treat patients with moderate to severe pain due to endometriosis unresponsive to first-line therapy with NSAIDs and hormonal contraception'. However, shortly after describing the patient population as such, ICER notes that 'the population of focus for this review is adult premenopausal women with symptomatic endometriosis'.*

- AbbVie recommends ICER consider that symptomatic endometriosis can be defined differently across the literature, and that the disease burden could differ by populations
- Various endometriosis patient populations have been evaluated in clinical trial publications of comparator treatments (e.g., GnRH agonist leuprolide). For example, several leuprolide trials enrolled patients with minimal or mild endometriosis-associated pain in addition to those with moderate to severe disease,[1,2] while others focused on patients with more severe forms of pain (e.g., endometriosis patients with persistent pain symptoms).[3-5]
- Women with moderate-to-severe endometriosis-associated pain have considerable unmet treatment needs. The severity of pain experienced by endometriosis patients correlates with health-related quality of life impairment, work productivity loss and economic burden.[6] In addition, higher pain or disease severity was found to be associated with higher rates of disease recurrence and surgery utilization.[7,8]
- Thus, due to the potential differences in treatment outcomes and disease burden between various endometriosis populations, we recommend that when assessing comparative treatment efficacy with elagolix, publications with comparable patient populations be selected.

Comparators: *AbbVie agrees with ICER's approach to compare elagolix to GnRH agonists, and recommends that leuprolide acetate depot be considered the primary comparator among all GnRH agonists. In addition, we suggest ICER to exclude the other considered comparators from the evaluation. AbbVie has the following considerations: 1) some listed comparators are not indicated for endometriosis; 2) the indicated population for elagolix are those who have not responded to NSAIDs and contraceptives (i.e., first-line therapies); and 3) goserelin, nafarelin, and danazol, while technically comparators to elagolix, are rarely used for endometriosis. Detailed rationales are listed below:*

- Hormonal contraceptives are not approved by the FDA for the treatment of endometriosis.[9] In addition, patients who have not responded to prior hormonal contraceptives will likely move on to second or third line therapies.
- Aromatase inhibitors are also not approved by the FDA for the treatment of endometriosis.[9] In addition, there is limited evidence supporting the efficacy of aromatase inhibitors in this patient population.[10]
- Goserelin, nafarelin and danazol are rarely used in real-world clinical practice. Based on findings from a U.S.-based claims study, <1% of endometriosis patients used goserelin or nafarelin and <1% of patients used danazol.[11]
- As identified by the ASRM, "Endometriosis is best viewed primarily as a medical disease with surgical back-up".[10] Therefore, surgery should not be considered as a comparator because the use of medical therapy does not preclude surgery. Moreover, the ASRM has recommended the use of selected medical therapies (e.g., GnRH agonists) after surgery.[10] More than half of the patients received at least one form of medical therapy within 1 year following the surgery.[12] Therefore, surgery should be included as an outcome in the model, not a comparator. In addition, surgery

and medical therapy are intended to impact endometriosis through different modalities, thus generating comparative evidence between the two can be challenging. In fact, the ASRM guideline concluded there was insufficient evidence to compare the medical versus surgical treatment of endometriosis, as no studies have directly compared the two approaches.[10] Lastly, multiple surgical procedures are used in endometriosis (e.g., laparoscopy, hysterectomy) with different outcomes and resource utilization.[12]

Response Definitions: *AbbVie suggests that ICER to consider the differences in pain scales, time frames used, pain types assessed, and response definitions across clinical trials in endometriosis. A few examples are provided below:*

- Pain reduction was typically evaluated as the primary outcome in the clinical trials. However, the trials used different pain scales to assess pain reduction, including the visual analog scale (VAS), numerical rating scale (NRS), the Biberoglu and Behrman (B&B) symptom scale, and modified B&B symptom scale. The B&B symptom scale or modified B&B symptom scale was developed specifically for endometriosis and assesses three distinct pain-related symptoms (dysmenorrhea, pelvic pain, and dyspareunia) as absent, mild, moderate, or severe (with a score of 0 reflecting absent symptoms and 3 reflecting severe symptoms), which may not be directly comparable with the VAS or NRS scale scores.[3-5,13-15] Further, the cutoff used to assess response among scales also varied between clinical trials.[3,4,14]
- The pain scales were also evaluated at different time points across clinical trials. Time points included daily assessments, 4-week recall periods for the B&B symptom scale, and assessments at 6-month intervals (e.g., at baseline and after 6 and 12 months of treatment).[3-5,13-15]
- Finally, different types of pain were assessed across clinical trials, including specific types of endometriosis-related pain such as dysmenorrhea, non-menstrual pelvic pain, and dyspareunia, as well as overall endometriosis-associated pain.[3-5,13-15]
- Due to the differences in scales, time points used, and the types of pain assessed, across clinical trials of endometriosis, the comparison of response rate across different treatments should be handled with caution. Direct comparisons without adjustments may not accurately reflect the true comparative effectiveness of treatments. In addition, we recommend that the types of pain related to endometriosis (e.g., dysmenorrhea and non-menstrual pelvic pain) be differentiated to capture the specific aspects of endometriosis symptoms.

Cost-Effectiveness Analysis (CEA) Model Structure*: ICER states that it will explore a model with a short-term decision tree (i.e., 6 months), followed by a long-term Markov model that has 4 states: disease-free, disease recurrence with retreatment, disease recurrence with surgery, and death. AbbVie recommends that ICER revise the model structure accordingly, as the current structure may be overly simplified and unable to fully capture the real-world clinical pathway for the target population. The detailed rationales are listed below:*

- ICER indicated the use of a published model by Sanghera et al. (2016)[16] that evaluated pharmaceutical treatments to "prevent recurrence of endometriosis following surgery" to inform the decision tree portion of the model and a published model by Wu et al. (2017)[17] for "preventing recurrent endometriosis after conservative surgery" to inform the Markov model health states. This seems to suggest that ICER intends to develop a post-surgical model; however, such a model would be contrary to the patient populations enrolled in the elagolix Phase III trials. In fact, women with a surgical history of hysterectomy, bilateral oophorectomy, procedure that interferes with gastrointestinal motility, or any recent major or minor surgery were excluded from the trials.[14] Thus, the current model structure and assumptions considered may not be fully applicable to the current evaluation.

- In real-world clinical practice, patients may use multiple lines of medical therapy or have multiple surgical procedures, and may also experience disease progression.[10,18] Therefore, considering a single health state for surgery and a single health state for medical retreatment may not be sufficient.
    - For example, surgery is generally not curative, with reoperation rates of 5.4% and 35.2% by 8 years following hysterectomy and laparoscopy, respectively.[19] When the use of medical therapy was also considered, the retreatment rates were 76.0% and 90.8% by 8 years following hysterectomy and laparoscopy, respectively.[19]
- AbbVie recommends ICER to consider the duration of the therapy when modeling the treatment cost since endometriosis drugs may be subject to limited recommended durations of therapy.[10,18] For example, based on FDA drug labels, duration of initial treatment or retreatment with leuprolide acetate depot should be limited to 6 months and depot medroxyprogesterone acetate (DMPA) treatment for longer than 2 years is not recommended.[20,21]
- AbbVie looks forward to seeing additional details in the analysis plan to describe the short-term decision tree, long-term Markov model health states, and how length of therapy will be incorporated in the model structure.

Comments on Key Outcomes, Health State Utilities, Long-Term Data, and Others:

- Table 1.2 of the draft scoping document has listed a number of key outcomes and key harms for evaluation. AbbVie looks forward to seeing additional details in the analysis plan regarding the data sources for these outcomes and how they will be incorporated in the evaluation. Other benefits and contextual considerations may be include: the value of oral therapy versus injection, the quality of the clinical trials, and the availability of long-term data.
- ICER lists fertility as a key outcome of interest. Because fertility outcomes were not typically assessed in the clinical trials of treatments for endometriosis, we recommend excluding this outcome from the evaluation due to lack of evidence.[3,4,14]
- ICER states that quality of life values will be included as key model inputs, and that health state utility values will be consistent across interventions. AbbVie looks forward to seeing the specific health state utility values to be included as well as ICER's approach to calculating quality-adjusted life years (QALYs) in the analysis plan.
- ICER states that the model time horizon will be until menopause onset. Given the lack of long-term data on many relevant outcomes for most endometriosis therapies, AbbVie recommends that ICER use caution in modelling these outcomes, and explore shorter time horizons (e.g. 1-year or 5-year). In addition, AbbVie would appreciate more details on the approach for modeling long-term outcomes in the analysis plan.

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Regarding 'The scoping document was developed with input from key stakeholders, including clinical experts, patients, and patient advocacy groups:'

Will there be a public list of such, as well as of their disclosures and conflicts of interests relative to Elagolix?

Concerns regarding the premise by which Elagolix is being promoted include the following --

Regarding 'Endometriosis is a chronic gynecological condition characterized by the attachment and proliferation of endometrial cells outside of the uterus:'

Endometriosis is indeed characterized by lesions comprised of endometrial glands and stroma; however, whilst the tissue somewhat resembles the native endometrium, it is not identical (Ahn et. al. 2016). This is a critical distinction, as an abundance of differential invasive, adhesive and proliferative behaviors have been demonstrated in the eutopic and ectopic counterparts of endometrial stromal cells in patients with the disease (Delbandi et al. 2013). Endometriosis lesions are functionally dissimilar from their eutopic counterparts (Zanatta 2010). The assumption that endometriosis results from normal endometrium that has 'wandered off' to aberrant sites and implanted itself as a result of retrograde menstruation sustains Sampson's near-century old theory. Were his theory wholly infallible, however, endometriosis would not be possible until menarche, yet there is evidence of disease in males (Jabr et al. 2014; Fukunaga et al. 2012; Giannarini et al. 2006; Zámečník et al. 2013; Pinkert et al. 1979; Martin Jr. et al. 1985; Schrodt et al. 1980; Beckman et al. 1985; Simsek et al. 2012, Oliker et al. 1971), the human fetus (Signorile PG, Baldi F, Bussani R, et al. 2009, 2010, 2012), and females who had never menstruated (Houston 1984). Retrograde periods also fail to account for extrapelvic disease. Moreover, although reflux menses is a very common phenomenon, not all individuals will develop endometriosis (Lagana et al.); the incidence of disease is small compared to the occurrence of backflow experienced by most menstruators (Ahn et al. a2015). Importantly, endometriosis is not an auto-transplant (Harara 2014; Signorile, Baldi 2010; Redwine 2002). It is critical to recognize these distinctions, particularly in a treatment discussion, as the continued propagation of endometriosis as normal tissue vis a vis Sampson's theory allows for poorly treated disease, promotion of anecdotal diagnoses and ongoing 'justifications' for non-excisional surgeries, empiric medical suppression that may actually be of no benefit, potentially needless hysterectomy and various other failed approaches to diagnosis and treatment.

Regarding 'empirical therapy is often initiated without surgery after other conditions are excluded:'

Contrary to popular presumption among non-specialists, endometriosis cannot be "excluded" without surgery. Normal exams do not exclude a diagnosis. Imaging appearances are characteristically nonspecific and operator-dependant, thus such modalities cannot be relied upon solely for diagnosis (Balleyguier et al. 2003; Chamié et al. 2011; Mukund et al. 2007; Takeuchi et al. 2005). It is simply not possible to triage individuals with chronic pelvic pain effectively on history or examinations alone; hence, those with suspected endometriosis will benefit from timely referral to specialist centers for careful clinical assessment and appropriate investigation (Ballard et al. 2010) - not simply placed on powerful medical therapy which can neither provide diagnosis nor necessarily efficacious treatment for the source of their pain.

Regarding 'Treatment recommendations have been developed by the American College of Gynecology and the American Society for Reproductive Medicine:'

Both organizations have historically eschewed Laparoscopic Excision (LAPEX) in favor of medical therapies and non-excisional surgeries and failed to support efforts to recognize endometriosis as specialty. Both are heavily supported by industry, which may or may not play a resulting role in the recommendations and positions they hold on the disease. Moreover, neither has updated said respective recommendations, which do not reflect modern concepts, in quite some time (despite encouragement to do so from the community). This is an important consideration.

Regarding 'For those with moderate or severe symptoms, pain management usually requires repeated courses of hormonal or surgical treatments until menopause:'

This reflects the common dogma surrounding endometriosis - a painful, expensive 'treatment' paradigm at that. However, this premise also assumes that all surgical procedures for endometriosis are performed by surgeons of similar experience and skill – they are not - and overlooks the wide disparity that actually exists. Such postulation does not

address the issue of completeness in removing all disease at the time of surgery and ignores the excellent results achieved by skilled excisionists with adequate experience in recognition and total resection of the disease. This may not always be reflected in the highly redundant literature on surgical aspects of the disease, as for the majority of high volume endometriosis surgeons in private practice, journal submissions are subsequent pursuits with clinical activity demanding all of their time and energy - yet most such Centers see tangible results in their patient populations daily. However, the literature still holds evidence of the significant improvements and effective long-term control of symptoms that can be achieved through meticulous surgical excision (Pundir et al. 2017; Rimbach, Ulrich, Schweppe 2013, et al. ad infinitum) alongside multidisciplinary adjuncts; further, such results are not dependent upon hormonal suppression; indeed, the value of post-interventional hormones remains inconclusive, however (M F A, Narwani, Shuhaila 2017; Yeung, Sinervo, Winer, Albee 2011).

Regarding 'a trial of a GnRHs agonist or laparoscopy to establish a definitive diagnosis prior to further treatment is considered:'

GnRHs are not equivalent to Laparoscopy and cannot establish a diagnosis. Medical therapy for patients with endometriosis aims principally toward the management of endometriosis-associated pain; they do not treat actual disease (Melis et al. 2016). The choice of 'which' medical treatment largely depends upon side-effect profiles, and all relieve pain associated with endometriosis equally (Swanton, McVeigh 2006). The premise that Laparoscopic confirmation is unnecessary and GnRH agonists may be used as a "therapeutic trial" is justified by very limited evidence; primarily – and unsurprisingly – by a consensus arrived at by a panel comprised largely of many advisors to the pharmaceutical sponsor (Gambone et al. 2002). A more recent study with similar conclusions, again connected to the sponsor, continues to recommend empiric treatment in patients "without evidence of severe disease," yet concedes that in order '[To] obtain more lasting relief, the majority of affected patients will need surgery, which allows not only for definitive diagnosis but also for the excision or ablation of visible lesions,' and admits that "[w]hen the medical therapy is discontinued, the risk of recurrence will be unchanged, only delayed for the duration of the therapy." The authors then mistakenly equate "resection or ablation of endometriosis" as equivalent techniques, citing surgery for the disease as "effectively [improving] symptoms in 80% of patients but only for 1 year," – yet simultaneously reference the Montpellier Consortium Consensus on current management of endometriosis vis a vis "excision of implants and ovarian cysts should be preferred over ablation..." (Lindsay et al. 2015).

Generally,

The potential for GnRH antagonist in endometriosis usage is not new. Cetrotide and Abarelix, for example, have been previously demonstrated to be effective in the treatment of pelvic pain caused by endometriosis, yet progress on at least one of the drugs is speculated to have been slowed by side effects (Elnasher 2015). At least one prior animal study on induced endometriosis demonstrated that leuprolide and cetrorelix were found to have similar efficacy in the regression of both the size and the histological structure of experimental endometriosis (Altintas et al. 2008). Another found that DMPA-SC and Elagolix demonstrated similar efficacy on endometriosis-associated pain (Carr et al. 2014). Specifically, first-in-human studies indicated that Elagolix may enable dose-related pituitary and gonadal suppression in premenopausal women as part of treatment strategies for endometriosis and other reproductive hormone-dependent disease states long ago (Struthers, Nicholls, Grundy et al. 2009). It is also already known through previous research that the immediate suppression of the pituitary achieved by GnRH antagonists without clinical flare is the main advantage of such compounds over the agonists (Schultze-Mosgau et al. 2005; Küpker et al. 2002).

Though the much touted benefit of GnRH antagonists is 'more tolerability/compliance and/or less side effects,' there is a dearth of side effect profiles in the literature to date specifically regarding Elagolix. Of those studies which do discuss potential negative effects, they are largely classified simply as 'tolerable' or otherwise not attributed to the drug itself. For example, in one study (for which AbbVie was asked to "review for accuracy the safety and efficacy data disclosed in this manuscript"), Elagolix demonstrated an "acceptable safety and tolerability profile" - yet the "serious adverse events" that occurred in the Elagolix groups were judged by investigators as "probably not associated to Elagolix." Further, in those cases where pregnancy occurred during treatment, one resulted in spontaneous abortion; two pregnancy-related serious adverse events occurred (cleft palate and tracheoesophageal fistula). Investigators again concluded that such outcomes were 'unlikely' to be related to Elagolix (Melis et al. 2016). This is surprising, considering the long history of GnRH class drugs as Category X.

In another editorial by one author long connected to GnRH studies, including those recommending expansion into adolescent endometriosis usage, adverse effects of Elagolix were noted to be "common but generally manageable" and cited as 'hot flashes, headaches, insomnia, mood swings, night sweats, slight increases in levels of total cholesterol, low-density lipoprotein cholesterol, triglycerides, high density lipoprotein cholesterol, and a significant decline in lumbar spine density over 6 months of use, particularly in the high dose groups; approaching the magnitude of bone loss seen in patients treated with GnRH agonists alone." The author concluded that although "[t]hese trials indicate clear benefits of Elagolix for endometriosis-associated pelvic pain, questions remain. The appropriate dose of Elagolix remains uncertain" (Hornstein 2017). Still others have concluded similarly, e.g. that in order to examine whether Elagolix can "compete with or even surpass established gold-standard medical treatments in this field, further studies that directly compare Elagolix to said treatments, might be necessary" (Perricos et al. 2017). Finally, it has been correctly stated that 'although Elagolix is a welcome addition to the endometriosis treatment paradigm…**Elagolix will garner uptake mainly from GnRH agonists, leaving the growing number of endometriosis patients in high need of new therapies."** (GlobalData Healthcare 2016).

The question begs then, is Elagolix really such a breakthrough, are its benefits superior to existing drug therapies, and are side effects indeed more tolerable?

Debate and semantics enshrouding current endometriosis doctrine notwithstanding, of greater concern is the potential conflict of interest in the literature from which assertions regarding efficacy and use of pharmaceutical therapies are drawn. That is to say: industry-sponsored research often draws pro-industry results (Bekelman et al. 2003). Relative to endometriosis specifically, Guo (2014) previously confirmed the existence of major methodologic drawbacks and overall limited transparency in the area of interventional trials for the disease. Vercellini unpacks this most eloquently, noting: "…specific trial outcome[s] may be selected among the possible ones, with the objective of favoring the drug under study; the trial design may be ''tailored'' to facilitate demonstration of the ineluctable significant difference; the study population may be inappropriately restricted, excluding those subjects in whom the new compound might reveal less effectiveness; a placebo instead of an active comparator may be chosen if the main trial objective is pain relief; a comparator with known major subjective and metabolic untoward effects may be preferred to one with a good safety and tolerability profile; clinical equivalence may be used as an excuse not to search for embarrassing differences; several data sets regarding different outcomes may be analyzed, publishing only favorable results and concealing unfavorable ones; multiple trials may be conducted, publishing only the results of those who demonstrated the superiority of the experimental drug" and, "if everything fails, study oblivion may constitute the best plan B." (Vercellini 2014). Case in point: most, if not virtually all, of the pro-Elagolix studies to date feature one of more of the following disclosures:

'Supported by AbbVie. | AbbVie was asked to review the manuscript for factual accuracy of the safety and efficacy data disclosed herein... | [ ] has received grant support from Neurocrine Biosciences, Inc. and has been a consultant for AbbVie, Inc... | [ ] are the recipients of research grants from AbbVie Pharmaceutical Company and [ ] has received speaker's fee from AbbVie... | Neurocrine Biosciences, AbbVie, and all authors participated in data analysis and interpretation. AbbVie provided funding for writing support…The authors and AbbVie reviewed and approved the article…Medical writing support was provided [ ] of AbbVie and [ ], contracted by AbbVie... | AbbVie reviewed and approved the manuscript and maintained control over the final content… | This study was funded by AbbVie Inc...The design and financial support for the study was provided by AbbVie Inc. AbbVie Inc. participated in data analysis, interpretation of data, review and approval of the manuscript. [ ] are AbbVie Inc. employees and may own AbbVie Inc. stock or stock options. [ ] was a paid scientific consultant for AbbVie Inc. in connection with this research project. [ ] served in a consulting role on research to AbbVie Inc. for this study.'

Henceforth, the question must be raised, is the future of Elagolix being shaped by associations between the industry and pro-industry conclusions? *Independent* evidence to date has not yet answered this or other questions about Elagolix, nor revealed whether or not it truly represents any 'progress' towards a cost-saving, effective measure with little negative impact on patients - or if it is just another variation on theme.

Respectfully submitted,
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1. The scope of evaluation seems broader than the potential indication for Elagolix which is for endometriosis-related pain. This is because one of the suggested key measures of clinical benefit is reproductive outcomes (Figure 1.1). On the other hand, the outcome of non-menstrual pelvic pain is included as an intermediate outcome (Figure 1.1). Additionally, in the report AIM section, we note "*the project will evaluate health and economic outcomes of elagolix for endometriosis*" and suggest adding a qualifier to align with the potential indication "*….of elagolix for treatment of endometriosis related pain*".
2. Figure 1.1, page 4. Suggested population is adult premenopausal women with symptomatic endometriosis. Should this be instead: adult premenopausal women with empiric endometriosis? Further, population should probably be limited to women with moderate to severe pain as measured by a pain measure.
3. Figure 1.1, page 4. Consider including congenital malformations as one of the adverse events.
4. Figure 1.1, page 4. Currently surgery is suggested as one of the comparators that may not be applicable since different treatment modality.
5. Figure 1.1, page 4. Title includes "anabolic" that seems a typo.
6. Populations, page 5. Should there be a lower limit for the age? For example, 15 or 18.
7. Table 1.2, page 5. Consider including the following in key harms: depression, vaginal dryness, decreased libido.
8. Table 1.1. page 6, Potential Other Benefits and Contextual Considerations. As the condition has dypareunia and the medication will produce vaginal dryness and libido decreased, it is important having partner's input.
9. Page 7. For the Marcov model, long term assessment based on "disease free" may not be applicable or appropriate since a surgery would be needed for such a health state, and more importantly, the correlation between symptoms and disease stage is poor.
10. Page 7. For the Marcov model, the challenge will be accessing long-term outcomes that have to be extrapolated from evidence not available in the Elagolix clinical program.
11. Page 7. For the economic model, NSAID is potentially not an appropriate comparator given lack of documented efficacy data.

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February 1, 2018

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: Society for Women's Health Research Input on Endometriosis

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 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, advocacy, and education.

Endometriosis presents one such example of a complex, heterogeneous estrogen-driven disorder associated with pelvic pain and infertility. Endometriosis occurs in about 6-10% of reproductive age women, and is most often diagnosed when they are in their 30s and 40s.[1]

An estimated two-thirds of women with endometriosis are symptomatic, while the remaining third may have no symptoms. Endometriosis symptoms can include painful menstrual cramps, pain in the lower back and pelvis, pain during or after sex, intestinal pain, painful bowel movements and urination during menstrual periods, bleeding or spotting between menstrual periods, and digestive problems. Infertility and reduced fecundity is also common,[2] with one study

[1] American Congress of Obstetrics and Gynecology. *Obstet Gynecol*. 2010;116(1):223-226.
[2] The Practice Committee of the American Society for Reproductive Medicine. *Fertil Steril*. 2012;98(3):591-598.

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finding that among the 71% of women with endometriosis who attempted to conceive, 90% experienced difficulties.[3]

On average, women with endometriosis make seven healthcare professional visits before seeing specialists, with an average diagnostic delay of 6.7 years, and nearly three-quarters of the women experiencing a misdiagnosis[4]. Among the reasons for delays in the diagnosis of endometriosis include: attitudes toward menstruation and the "normalization" of pain by women, their mothers, and healthcare providers; nondiscriminatory exams (both digital examination and transvaginal ultrasound); intermittent use of contraception causing hormonal suppression; and misdiagnosis.[5] As a result, patients suffering from endometriosis may experience stigma, including feelings of discomfort about themselves or negative reactions from others, which can prevent patients from getting appropriate care, treatment, and compassion.

As a stigmatized disease that solely impacts women in their prime working and childbearing years, the burden of endometriosis has significant negative effects. Endometriosis often causes issues in performing daily tasks such as household chores; and can negatively impact sexual relations, productivity in the workplace, appetite, exercise, and sleep.[6] Total productivity loss in employed women with endometriosis averages 6.3 hours per week, with the majority of lost productivity due to presenteeism.[7]

Due to stigma and lack of information about the disease, many healthcare providers do not adequately or appropriately treat endometriosis. In the most extreme example, some women with endometriosis have hysterectomies at a young age, many of which are medically unnecessary. The burden of endometriosis is further complicated by comorbid conditions including depression, anxiety, autoimmune and endocrine disorders, and migraine,[8,9,10] which impacts diagnosis, treatment, and cost of a disease that has not seen innovation in decades.

New diagnostic and therapeutic options have the potential to improve health quality significantly for patients, and thus reduce the social and economic burdens associated with this complex, estrogen-driven disease. We appreciate ICER's intent to employ a patient-centered (in this case, female-centered) approach when assessing the value and effectiveness of new treatment options. We urge ICER to use progressive modeling techniques that capture the indirect costs of the stigma and societal burden of this debilitating estrogen-driven condition and the cost benefit of gains in functioning associated with treating endometriosis to improve a woman's management of co-morbid conditions, such as those identified above.

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[3] Fourquet et al. *Fertil Steril*. 2010;93(7):2424-28. doi: 10.1016/j.fertnstert.2009.09.017.
[4] Nnoahahm et al. *Fertil Steril*. 2011 Aug;96(2):366-373.e8. doi: 10.1016/j.fertnstert.2011.05.090.
[5] Hudelist et al. *Hum Reprod*. 2012 Dec;27(12):3412-6. doi: 10.1093/humrep/des316.
[6] Fourquet et al. *Fertil Steril*. 2010;93(7):2424-28. doi: 10.1016/j.fertnstert.2009.09.017.
[7] Soliman et al. *J Manag Care Spec Pharm*. 2017;23(7):745-754.
[8] Laganà et al. *Int J Womens Health*. 2017;9:323–330.
[9] Sinaii et al. *Hum Reprod*. 2002 Oct;17(10):2715-24.
[10] Tietjen et al. *Headache*. 2007 Jul-Aug;47(7):1069-78.

SWHR appreciates the opportunity to provide the above input and we look forward to serving as a resource to ICER on a range of chronic conditions affecting women.

If you have questions or if we can provide further information to inform ICER's analysis, 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