abbvie

Comments on ICER's Draft Evidence Report of "Elagolix for Treating Endometriosis"

AbbVie appreciates the opportunity to provide comments on the draft evidence report "Elagolix for Treating Endometriosis", which was posted by ICER on its website on May 4, 2018. AbbVie recommends that ICER considers the following when developing their final evidence report.

Comments on ICER's comparative clinical effectiveness evaluation

ICER's rating on the comparative net health benefit of elagolix should be revised

- ICER assigns a rating of P/I (promising but inconclusive) for the comparative net health benefit of elagolix versus placebo (Table 3.12). AbbVie disagrees with this rating based on the strong evidence for the efficacy and safety of elagolix for endometriosis.
  - The Elaris Endometriosis I and II (EM-I and EM-II)[1,2] trials are the largest to date to study endometriosis and its treatments, and have been judged to be of good quality by ICER (page 22). Even in the Phase II trials (e.g., Tulip-PETAL[3] and Lilac-PETAL[4]) that used slightly different efficacy measures, significant benefits of elagolix versus placebo were observed.
  - Significant benefits were observed comparing elagolix versus placebo across several outcome measures (i.e., dysmenorrhea [DYS] response, non-menstrual pelvic pain [NMPP] response, secondary pain outcomes, quality of life and analgesic use) in the pivotal Phase III trials Elaris Endometriosis I and II (EM-I and EM-II).[1,2]
  - There were no significant differences in serious or severe adverse events (AEs) between the elagolix and placebo arms in the EM-I and EM-II trials.[1] In addition, elagolix is not associated with a sustained reduction in bone mineral density (BMD), an hypoestrogenic-induced AE, after treatment discontinuation. In the long-term extension studies EM-III and EM-IV, lumbar spine, hip and femoral neck BMD assessments showed progressive recovery towards baseline and Z-scores remained within normal values for age-matched population during the post-treatment follow-up period.[5,6] Further, short-term BMD loss does not correlate one-to-one with increased fracture risk; prior research has found that the overall proportion of fractures attributable to low BMD is modest.[7,8]

Comments on modeled elagolix treatment

The elagolix 150 mg QD dose should be considered

- Only elagolix 200 mg twice daily (BID) is considered in ICER's economic evaluations. However, two different doses were evaluated in the EM-I and EM-II clinical trials, i.e., 150 mg once daily (QD) and 200 mg BID, and both were submitted to the FDA for review.[1] AbbVie recommends that ICER consider both elagolix doses in its economic evaluations.

A maximum duration of continuous elagolix treatment should be considered

- ICER's cost-effectiveness (CE) model assumes that patients in the reduced pain state use elagolix continuously until pain recurrence, surgery, or pregnancy. By not limiting the elagolix treatment duration, ICER's evaluation could lead to a model in which women may still be on elagolix treatment after 18 years. This is unlikely be to the case in clinical practice.

Comments on the CE model structure

Elagolix for dysmenorrhea and non-menstrual pelvic pain should be modeled together

- ICER evaluates elagolix in separate CE models for the DYS and NMPP outcomes. AbbVie does not think this is an appropriate way to model endometriosis outcomes and recommends that ICER update the model to evaluate both response measures together in the same model, using reasonable assumptions to weigh and combine the two response measures as needed.

- First, endometriosis is coded as one disease with an ICD-10 code of N80.X, with the X specifying the location of the endometriosis and not the pain symptom. As such, the clinical reality is that endometriosis-related DYS and NMPP are treated as one disease.
- Second, evaluating the two pain symptoms separately underestimates the value of elagolix treatment. In a given month, patients could experience DYS during their menstrual period and NMPP during the rest of the month, such that they could garner treatment benefits for both pain symptoms over the month. Therefore, an evaluation of elagolix for DYS alone captures only a portion of its value over a month and vice versa for an evaluation of elagolix for NMPP alone. Indeed, only by evaluating DYS and NMPP together could a model capture 100% of the value of elagolix.
- Finally, the fact that DYS and NMPP are symptoms of one disease is further reflected in one of the inclusion criteria to the elagolix Phase III trials EM-I and EM-II: patients were required to have at least 2 days of moderate or severe DYS **and** NMPP during that last 35 days in the screening period.[1]

Receipt of add-on treatment(s) following surgery should be considered

- In ICER's model, women in post-surgery health states would not receive any active add-on treatment except for analgesics. AbbVie does not believe this reflects the real-world treatment patterns for endometriosis and suggests that ICER allow receipt of additional add-on treatment(s) for the post-surgery states to be more aligned with real-world treatment patterns for endometriosis.
  - The ASRM guideline recommends medical add-on therapy using hormonal therapies (e.g., GnRH inhibitors, combined oral contraceptives) following the surgical procedures to prolong the benefits of surgery and manage symptoms. The recommended duration for the add-on treatment is 6 months.[9]
  - Surrey et al. 2017 reported that 25.2%, 11.6% and 22.8% of patients used combined oral contraceptives, GnRH agonists, and progestin, respectively, within 12 months after undergoing laparoscopy; and 1.0%, 0.5%, and 3.0% of patients used combined oral contraceptives, GnRH agonists, and progestin, respectively, within 12 months after undergoing hysterectomy.[10]

Probability of hysterectomy without prior laparoscopy should be considered

- ICER assumes that hysterectomy could only occur as a repeat (i.e., after laparoscopy) and final surgery. However, in the real world, patients may have hysterectomy without prior laparoscopy. Per Table 3 of Soliman et al. 2016, 11.7% of patients received hysterectomy in the one-year following leuprolide acetate treatment, while only 4.2% received laparoscopy, suggesting that some patients received hysterectomy without prior laparoscopy.[11] As such, AbbVie recommends that ICER include the probability of hysterectomy without prior laparoscopy in the model.

Recurrence of pain symptoms after successful surgery should be considered

- ICER assumes that women who experienced successful surgery enter the post-surgery with reduced pain (M4) state and remain there indefinitely. However, this is not consistent with real-world observations, where recurrence of pain symptoms after surgery is not insignificant.[12-16] This issue is exacerbated with the long model time horizon.

Comment on cost-effectiveness model inputs

More comprehensive surgical procedure unit costs should be considered

- Per Table F2, the unit costs for laparoscopic surgery and hysterectomy per event used in the model were $5,433 and $14,437, respectively, based on Fuldeore et al. 2011.[17] AbbVie believes

the current inputs underestimate the surgery cost as they do not comprehensively capture the costs associated with the surgical procedures and associated complications. Based on Surrey et al. 2017, 36-46% of patients experienced complications associated with laparoscopy or hysterectomy surgeries.[10] The increased healthcare resource utilization has been observed up to one year after the surgical procedure due to the complications.[10]

- For the surgery costs, AbbVie suggests using data on file from Soliman et al. 2017, who evaluated the 3- to 12-month healthcare expenditures following different surgical procedures among endometriosis patients using US insurance claims data.[18] Total healthcare expenditures in 2014 USD over the 3-month period following the surgical procedure were estimated to be $10,625 ($10,428 paid by the plan) for laparoscopy and $14,590 ($14,411 paid by the plan) for hysterectomy.[19] These 3-month costs on file are provided for ICER to use in their model with a 3-month cycle length.

Costs of productivity loss may be underestimated

- Per Table 4.6, ICER derives the costs of productivity loss for patients with moderate to severe symptoms as average hourly wage multiplied by the total absenteeism hours reported for the overall endometriosis population in Soliman et al. 2017.[20] AbbVie believes this approach underestimates the costs of productivity loss and suggests the following modifications.
  - First, productivity loss should include both absenteeism and presenteeism. Results from Soliman et al. 2017[20], Diamond et al. 2018[21], and Nnoaham et al. 2011[22] suggest that presenteeism is the major component of productivity loss in the workplace for patients suffering from endometriosis.
  - Second, productivity impacts should be estimated using total compensation (i.e. wages plus benefits). This would follow the best practices for calculating productivity impacts into CE analyses.[23] Based on the US Bureau of Labor Statistics, the total employer cost averaged $35.87 per hour worked, which includes $24.49 for wages and salaries and $11.38 for benefits.[24]
  - Third, the ICER model uses 13.2 hours lost due to productivity per 3-month period. This estimate was calculated by multiplying the weekly average absenteeism loss across all patients (1.1 hours) from Soliman et al. 2017 by 12.[20] However, the 1.1 hours was for all patients, including those with mild symptoms. A more relevant estimate of weekly productivity hours lost for patients with moderate to severe pain could be obtained from the weekly estimated productivity loss at baseline from the elagolix Phase III trials.[21] The results from the ISPOR 2018 poster suggest that patients with moderate to severe symptoms lost about 2.5-3.4 hours and 11.6-14.8 hours due to absenteeism and presenteeism, respectively.
  - Fourth, the ICER model allocates productivity costs to the proportion of women in moderate-to-severe pain health states and not to those in the reduced pain states. This is not consistent with the findings of Soliman et al. 2017, where even women with mild endometriosis symptoms reported positive hours of lost employment (1.9 hours/week total) and household productivity (2.5 hours/week total).[20]
  - Finally, costs of household productivity loss should also be included in the total costs of productivity loss. Data supporting these costs are also available from Soliman et al. 2017.[20]

Surgical procedure disutility values are unclear

- The disutility parameters associated with laparoscopy and hysterectomy in the model are -0.06 and -0.07, respectively. These values were obtained from Ganz, et al. which in turn derived them from Roberts et al.[25,26] However, the process by which these values were derived is not clear.

These values conflict with prior studies, which have found the disutility of hysterectomy to be substantially larger than -0.07.[27,28] Additionally, it is unclear that the disutility values associated with laparoscopy and hysterectomy are essentially equal when one procedure is significantly more invasive than the other.

Risk of fracture may be overestimated

- Per Table F4, ICER uses a relative risk of fracture for women of 1.5 per one standard deviation decrease of Z-score in BMD based on Kanis et al. 2001.[29] The baseline osteoporotic fracture risk used by ICER was derived from Looker et al. 2017 among women aged 40-49 years.[30] AbbVie disagrees with the approach used by ICER because both references predominantly focused on older women in the postmenopausal age range, while the target population is much younger (median age 32 years).
- In addition, elagolix is not associated with a sustained reduction in BMD after treatment discontinuation. In the long-term extension studies EM-III and EM-IV, lumbar spine, hip, and femoral neck BMD Z-scores progressively moved towards baseline values during the post-treatment follow-up period.[5,6]
- AbbVie suggests that ICER remove fracture risk as a long-term AE in the evaluation.

Comments on potential budget impact analysis

AbbVie respectfully provides some feedback on ICER's BI analysis of elagolix specifically below and suggests that ICER revise its analysis.

- Prior critiques of the ICER approach have found that adhering to a product-level spending cap requires that approximately one-third of new drug spending be reallocated to other goods and services that could potentially be less cost-effective due to significant barriers to information.[31] In the case of elagolix, which ICER finds to be cost-effective, this could produce tremendous inefficiency.
- A BI threshold approach punishes treatments of highly prevalent diseases like endometriosis, and therapies that meet a high unmet need like elagolix.[32]
- For many women, as recognized by ICER on page 62 of the evidence draft report: "Elagolix is most likely to be considered as an alternative to GnRH agonists. The most commonly used GnRH agonist, leuprorelin acetate, is given by monthly injection."[33] However, treatment substitution effects were not accounted for in ICER's model, despite that they would affect the payer's pharmaceutical budget. This contradicts the review of treatment options and clinical guidelines conducted by ICER (Section 2.2, page 11). Excluding substitutes unrealistically penalizes elagolix in the BI threshold approach, since the underlying assumption that all patients would otherwise have received watchful waiting is not supported by real-world claims data.[34,35]
- ICER BI calculation excludes cost offsets outside of the pharmacy budget from its analysis; this penalizes therapies that reduce medical costs (e.g., surgeries and hospitalizations) but not pharmacy benefit. ICER's elagolix CE model shows elagolix cost offsets related to fewer surgeries (Tables 4.7 and 4.8), however, this cost offset is not factored into the BI threshold calculation. If payers had a product level spending cap, it should consider cost offsets related to reduced surgeries calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care event as stated on page 66 of the evidence draft report.[33]
- ICER evidence draft report does not present some of the information provided in ICER's analytic plan.[36] The missing information include the number of outpatient visits, the cardiovascular

disutility, and information on the rescue pain agents (e.g., drug, dosage, utilization, and cost). AbbVie suggests that ICER provides detailed information on the model inputs used in their CE and BI models.

- ICER's CE model assesses elagolix effects over an 18-year horizon, while BI is focused on a much shorter time horizon. The theoretical basis for these different time horizons in CE and BI models is unclear.

A comment on the threshold price calculation

- There appears to be an inconsistency in the report regarding the threshold price analysis present within Table 4.16. First, ICER assumes the price to be $7,000 per year ($583 per month) and calculates that the cost per QALY for NMPP (short run) at this price is $146,779. ICER then states that the price would need to be $578 per month to match the $150K per QALY threshold. If the price is lowered, cost per QALY should go down, not up, contradicting the threshold analysis results. AbbVie recommends a careful review of the calculations which led to these results.

Suggested corrections, organized by Table or Figure numbers

Item	Current Values	Corrected Values; References and Notes
P23-24, "In EM-I, 150 mgs daily dose elagolix provided a 14% difference from placebo in clinical response on [NMPP] (97.5% CI, 18 to 35) at three months and 11% (97.5% CI, 10 to 28) at six months."	(97.5% CI, 5 to 35) and (97.5% CI, 10 to 28)	(97.5% CI, 5 to 23) and (97.5% CI, 2 to 20); Taylor et al. 2017, Figure 1.1[1]
Table 3.5 Placebo of Lilac PETAL	Please consider both placebo arms in the trial: Placebo/Elagolix 150mg and Placebo/Elagolix 250mg; Diamond et al. 2014.[4]	
Table 3.8 VAS score, DMPA-SC, week 24	-22.8	-17; Carr et al. 2014, Supplemental Figure 2.[37]
Table 3.8 VAS score, Elagolix 75 BID, week 24	-26.8	-23.6; Carr et al. 2014, Supplemental Figure 2.[37]
Table 3.9 Leuprorelin Acetate column	Wrong source was referenced. The right source should be FDA prescribing information 2018.[38]	
Appendix E. Diamond 2014, Percent days with prescription analgesic use	-2.4	-2.6; Diamond et al. 2014, p. 366.[4]
Appendix E, Acs N. 2014, NMPP (digitalized) Mean Change (SE)	6 months	3 months; Ács et al. 2014, Figure 1.[3]

References

1. Taylor HS, Giudice LC, Lessey BA, et al. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. *New England Journal of Medicine.* 2017;0(0):null.
2. Agarwal S, Soliman AM, Schwefel B, Peloso P, Surrey ES, Taylor HS. Impact of Elagolix on Health-Related Quality of Life Among Patients With Moderate to Severe Endometriosis-Associated Pain: Analysis of EQ-5D-5L Data From a Phase III Randomized Controlled Trial. Poster presented at ISPOR 2018; 2018; Baltimore, MD.
3. Ács N, O'Brien C, Jiang P, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist: results from a phase 2, randomized controlled study. *Journal of Endometriosis and Pelvic Pain Disorders.* 2015;7(2):56-62.
4. Diamond MP, Carr B, Dmowski WP, et al. Elagolix treatment for endometriosis-associated pain: results from a phase 2, randomized, double-blind, placebo-controlled study. *Reprod Sci.* 2014;21(3):363-371.
5. Archer D, Watts N, Duan WR, Peloso P, Wang H, Chwalisz K. Long-term Effect of Elagolix on Bone Mineral Density in Women with Endometriosis-Associated Pain [38G]. *Obstetrics & Gynecology.* 2018;131.
6. Archer DF, Watts N, Gallagher C, et al. Long-term effect of elagolix on bone mineral density: results from two phase 3 extension studies in women with endometriosis-associated pain. *Fertility and Sterility.* 2017;108(3):e95.
7. Stone KL, Seeley DG, Lui LY, et al. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. *J Bone Miner Res.* 2003;18(11):1947-1954.
8. Trémollieres Florence A, Pouillès JM, Drewniak N, Laparra J, Ribot Claude A, Dargent‐Molina P. Fracture risk prediction using BMD and clinical risk factors in early postmenopausal women: Sensitivity of the WHO FRAX tool. *Journal of Bone and Mineral Research.* 2010;25(5):1002-1009.
9. Treatment of pelvic pain associated with endometriosis: a committee opinion. *Fertil Steril.* 2014;101(4):927-935.
10. Surrey ES, Soliman AM, Yang H, Du EX, Su B. Treatment Patterns, Complications, and Health Care Utilization Among Endometriosis Patients Undergoing a Laparoscopy or a Hysterectomy: A Retrospective Claims Analysis. *Advances in therapy.* 2017;34(11):2436-2451.
11. Soliman AM, Bonafede M, Farr AM, Castelli-Haley J, Winkel C. Analysis of Adherence, Persistence, and Surgery Among Endometriosis Patients Treated with Leuprolide Acetate Plus Norethindrone Acetate Add-Back Therapy. *Journal of managed care & specialty pharmacy.* 2016;22(5):573-587.
12. Soliman AM, Bonafede M, Farr AM, Castelli-Haley J, Winkel C. Analysis of subsequent surgery rates among endometriosis patients who underwent surgery with and without concomitant leuprolide acetate therapy. *Current medical research and opinion.* 2016;32(6):1073-1082.
13. Soliman AM, Du EX, Yang H, Wu EQ, Haley JC. Retreatment Rates Among Endometriosis Patients Undergoing Hysterectomy or Laparoscopy. *Journal of women's health (2002).* 2017;26(6):644-654.
14. Koga K, Takemura Y, Osuga Y, et al. Recurrence of ovarian endometrioma after laparoscopic excision. *Hum Reprod.* 2006;21(8):2171-2174.
15. Rizk B, Fischer AS, Lotfy HA, et al. Recurrence of endometriosis after hysterectomy. *Facts, Views & Vision in ObGyn.* 2014;6(4):219-227.

16. Shakiba K, Bena JF, McGill KM, Minger J, Falcone T. Surgical treatment of endometriosis: a 7-year follow-up on the requirement for further surgery. *Obstetrics and gynecology.* 2008;111(6):1285-1292.
17. Fuldeore M, Chwalisz K, Marx S, et al. Surgical procedures and their cost estimates among women with newly diagnosed endometriosis: a US database study. *Journal of medical economics.* 2011;14(1):115-123.
18. Soliman AM, Taylor H, Bonafede M, Nelson JK, Castelli-Haley J. Incremental direct and indirect cost burden attributed to endometriosis surgeries in the United States. *Fertility and Sterility.* 2017;107(5):1181-1190.e1182.
19. AbbVie Inc. AbbVie data on file (H18.DoF.012 ABBV-US-00002-HEOR). 2018.
20. Soliman AM, Coyne KS, Gries KS, Castelli-Haley J, Snabes MC, Surrey ES. The Effect of Endometriosis Symptoms on Absenteeism and Presenteeism in the Workplace and at Home. *Journal of managed care & specialty pharmacy.* 2017;23(7):745-754.
21. Diamond MP, Soliman AM, Snabes MC, Gordon K, Wang H, Coddington C. Productivity Gains Associated with Treatment with Elagolix for Endometriosis-associated Pain. Poster presented at ISPOR 2018; 2018; Baltimore, MD.
22. Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril.* 2011;96(2):366-373.e368.
23. Lakdawalla DN, Doshi JA, Garrison LP, 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 in Health.* 2018;21(2):131-139.
24. Bureau of Labor Statistics. Employer costs for employee compensation – December 2017. *Economic News Release* 2018; https://www.bls.gov/news.release/pdf/ecec.pdf. Accessed May 15, 2018.
25. Ganz ML, Shah D, Gidwani R, et al. The cost-effectiveness of the levonorgestrel-releasing intrauterine system for the treatment of idiopathic heavy menstrual bleeding in the United States. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2013;16(2):325-333.
26. Roberts TE, Tsourapas A, Middleton LJ, et al. Hysterectomy, endometrial ablation, and levonorgestrel releasing intrauterine system (Mirena) for treatment of heavy menstrual bleeding: cost effectiveness analysis. *BMJ (Clinical research ed).* 2011;342.
27. Harris RA, Washington AE, Nease RF, Jr., Kuppermann M. Cost utility of prenatal diagnosis and the risk-based threshold. *Lancet (London, England).* 2004;363(9405):276-282.
28. Chung A, Macario A, El-Sayed YY, Riley ET, Duncan B, Druzin ML. Cost-effectiveness of a trial of labor after previous cesarean. *Obstetrics and gynecology.* 2001;97(6):932-941.
29. Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporos Int.* 2001;12(12):989-995.
30. Looker AC, Sarafrazi Isfahani N, Fan B, Shepherd JA. FRAX-based Estimates of 10-year Probability of Hip and Major Osteoporotic Fracture Among Adults Aged 40 and Over: United States, 2013 and 2014. *National health statistics reports.* 2017(103):1-16.
31. Ciarametaro M, Abedi S, Sohn A, Ge CF, Odedara N, Dubois R. Concerns Around Budget Impact Thresholds: Not All Drugs Are the Same. *Value in Health.* 2017;20(2):230-233.
32. Neumann PJ, Cohen JT. ICER's Revised Value Assessment Framework for 2017-2019: A Critique. *PharmacoEconomics.* 2017;35(10):977-980.
33. Institute for Clinical and Economic Review, New England Comparative Effectiveness Public Advisory Council. Elagolix for Treating Endometriosis. *Draft Evidence Report;*2018.

34. Soliman AM, Yang H, Du EX, Kelley C, Winkel C. The direct and indirect costs associated with endometriosis: a systematic literature review. *Hum Reprod.* 2016.
35. National institute for Health and Care Excellence. Endometriosis: diagnosis and management. *NICE guideline [NG73]*. London: National institute for Health and Care Excellence; 2017.
36. Institute for Clinical and Economic Review, New England Comparative Effectiveness Public Advisory Council. Endometriosis: Model Analysis Plan. 2018.
37. Carr B, Dmowski WP, O'Brien C, et al. Elagolix, an oral GnRH antagonist, versus subcutaneous depot medroxyprogesterone acetate for the treatment of endometriosis: effects on bone mineral density. *Reprod Sci.* 2014;21(11):1341-1351.
38. AbbVie. Lupron Depot: Highlights of Prescribing Information. 2018; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020708s035lbl.pdf. Accessed May 24, 2018.

May 31, 2018

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Evidence Report "Elagolix for Treating Endometriosis"

Dear Dr. Pearson:

Patients Rising Now appreciates the opportunity to provide our comments on ICER's May 4th draft evidence report, "Elagolix for Treating Endometriosis."

Patients Rising Now advocates on behalf of patients with life-threatening conditions and chronic diseases for them to have access to vital therapies and services. Access to treatments provides survival and improved quality of life for those patients. We believe access spans affordability, insurance coverage, and physical access. We analyze information and publicly communicate those analyses to engage patients, caregivers, physicians, the media, health policy experts, payers, providers and other health professionals, to foster realistic, patient-centered, solution-oriented discussions so that those facing critical medical needs can amplify their collective voice to create lasting improvements for health in the United States. That is, our goal is to advance a balanced dialogue that illuminates the truth about health care in a just and equitable manner.

Patient perspectives about endometriosis are complicated. The pain and personal consequences of endometriosis (e.g., infertility, pain with intercourse), are very challenging to evaluate and treat. ICER's draft report, in part because it evaluates one unapproved potential therapy, contains limited data on real-world effectiveness, as well as critical patient factors and perspectives, which raises numerous concerns about the draft report. Our patient-focused comments about this report are below, organized into sections about Patient Perspectives and Complexity, Cost Considerations and Analyses, and Technical Notes.

Patient Perspectives and Complexity

Patient Perspectives

By not adequately incorporating the qualitative and very important aspects of women's perspectives related to endometriosis and potential treatment options, ICER's draft report diminishes the importance to women with endometriosis of improved function and quality of life in several ways.

First, the draft report recognized that "elagolix is taken daily as an oral formulation. This is likely to be viewed favorably by patients, as it may reduce healthcare complexity for women compared to GnRH agonists that are delivered via nasal spray or in-office intramuscular injections, or who are considering the potential for complications and time to recover from surgery."[i] And the draft report goes on to further state that "in contrast to GnRH agonists, elagolix does not produce the

"flare" or surge in hormones that leuprorelin acetate causes in the first few weeks of treatment. The flare can often lead to increased menstrual bleeding and other side effects that some women described as being uncomfortable."[ii]

The fact that ICER recognizes those aspects of endometriosis and the potential qualitative benefits of elagolix is additionally distressing since the draft report also finds that women with endometriosis have noted their "…perception that health care providers are not taking their complaints seriously."[iii] We point this out because, as discussed below, it also seems that ICER is not taking the real life implications of endometriosis for women with this condition – and their families – seriously enough.

Complexity of Endometriosis and Patient Experiences

While the specific anatomical pathology of endometriosis is relatively straight-forward (i.e., the presence of endometrial tissue at locations other than the uterus), the reproductive hormonal/endocrine system for a premenopausal woman is very complex. As one review article described it, "Given the complex nature and likely multifactorial etiology of endometriosis pathogenesis, a vast number of pharmacologic target options exist. Strategies for medical intervention include drugs that suppress ovulation and/or induce a hypoestrogenic state, medications that act directly on endometriotic deposits, anti-inflammatory agents, and immunomodulators."[iv] We also note that this article discusses several additional treatment options not discussed in ICER's draft report, and we concur with its conclusion that FDA-approved and ''off-label'' treatments for endometriosis, "are complementary to each other in the individualized care for this complex and challenging disease."[v]

The complexity of treating endometriosis was also highlighted in a review of clinical guidelines published in November 2017 (which ICER did not appear to include in its analysis) that found only 10 of 152 recommendations were common across the seven guidelines assessed. We also found striking that the authors of this review explicitly stated in their publication that they "involved a woman with endometriosis in the design and delivery of our research,"[vi] something that ICER apparently did not do.

Cost Considerations and Analyses

Our first concern about the draft report's cost effectiveness analyses is the information about lost productivity. For example, the data included in Table 4.6 on page 50 are perhaps the minimum figures that could be derived from the available sources and excluding the full scope of productivity cost data related to endometriosis leads to skewed and biased conclusions in the draft report. Specifically:

- The "Average Hourly Wage" in Table 4.6 only represents actual wages to individuals. However, this section is titled "Societal Perspective Inputs" – and the Bureau of Labor Statistics (BLS) data on total compensation is what other researchers have used for their productivity calculations.[vii] Therefore, we believe ICER should also use that data point since it more accurately reflects the total marginal cost to an employer for each employee. And for December 2017, BLS reported that amount to be $35.87/hour,[viii] rather than the $24.34/hour wage number ICER chose to use.

- In the second row of Table 4.6, while ICER lists 13.2 hours lost/3 months, that number is inconsistent with (and much lower than), what has been reported elsewhere. Specifically, the 2017 article by Soliman et al.,[ix] which compared women with endometriosis to controls, calculated that women with endometriosis lost per week 1.1 hours of employment productivity from absenteeism and 5.3 hours from presenteeism – and an additional 4.8 hours in household productivity. Thus, using Soliman's data, lost workplace productivity in Figure 4.6 would be 83.2 hours for every three months, and a total lost productivity of $11,937.54 per year. In addition, an even higher figure could be discussed for the lost work productivity from endometriosis since we assume the $15,000/year amount cited on page 1 of the draft report is from the 2011 prospective study by Nnoaham et al. of women scheduled for laparoscopy, which reported lost productivity in the USA from endometriosis of $15,737/year in 2007 dollars[x] – and thus the equivalent 2018 amount would be significantly higher.

Therefore, we urge ICER to recalculate its Societal Perspectives analysis using total compensation (rather than only wages), and update lost time figures to reflect – at a minimum – both workplace presenteeism and absenteeism. We believe more accurate data inputs would demonstrate Soliman's conclusions that "In comparison with other conditions, women with endometriosis have reported greater work productivity and activity impairment than patients with conditions such as rheumatoid arthritis. Furthermore, the absenteeism rates reported in this study are higher than those reported for other pain conditions such as headaches and back pain."[xi]

Second, we concur with ICER's finding that the "short duration of therapy with elagolix versus placebo or other active comparators means it is difficult to extrapolate the benefits and risks of long-term use. Available comparative data assessed elagolix versus placebo at three or six months."[xii] Similarly we concur with ICER evidence rating for Elagolix of "Promising but Inconclusive" – given that it is the first medicine with this mechanism of action and has yet to be approved by the FDA, that finding is far from surprising. However, this degree of uncertainty also leads to significant uncertainty in the draft report's conclusions. For example, we observed that because of the small incremental QALY's in ICERs calculations any changes to that finding – such as slight modifications to the calculated social impact (e.g. productivity) – results in large difference in incremental QALYs.[xiii] This is also illustrated in the Sensitivity Tornado analyses in Figures 4.2, 4.3, 7.1 and 7.2. We also believe that the uncertainty illustrated by the sensitivity analysis should be highlighted in the body of the report rather than relegated to the end. This would better reflect the perspectives of women with endometriosis where there is so much individual variability and uncertainty about their clinical situation and options.

And third, by evaluating a medicine before it has been approved by the FDA means that not only is the manufacturer's list price unknown, but the label indications and warnings are also unknown. We recognize that to determine a "placeholder" for price, ICER uses the "projected price" from Seeking Alpha a "financial market research firm,"[xiv] which is a free and publicly available news source. However, there are many other proprietary market research firms in the competitive business of projecting prices and other financial aspects of potential therapies before FDA approval. Has ICER consulted any of those analyses before picking the publicly available free option?

We raise these points because ICER's "health system"[xv] and "third party payer"[xvi] perspectives, puts ICER into the role of purchaser – or advisor to purchasers and payers – rather than value analyst. In other words, ICER seems to be declaring that if the launch price is above what ICER determines as "just" then the company and its product should be shunned – irregardless[xvii] of the clinical benefit the therapy would bring to patients, and ignoring the very diverse set of patient populations and payers in the US and their range of value considerations based upon their structure, governance, and enrollee population – an inherent complexity of the U.S. health care financing system that ICER's draft report doesn't address.

Technical Notes

We want to bring to your attention several technical issues in the draft report that you may want to address before it is finalized:

- Reference #37 has an incorrect link to NICE document. The correct link is https://www.nice.org.uk/guidance/ng73#
- On page 43, the draft report indicates that Excel is from "Redmond, VA". We suspect that it is a proofreading error, and that it should be "Redmond, WA" which is where Microsoft, the producer of Excel as part of the Microsoft Office Suite is headquartered. An additional aspect of this that would be helpful for ICER to clarify is what version of Excel was used to run the model as well as what computer system and CPU were used. Given that there have been problems with both the use of Excel for computational models (e.g., Harvard Economics Professors misusing Excel published erroneous analyses and conclusions[xviii]), and computer CPUs that produced incorrect calculation,[xix] we think ICER should include those technical specifications in its reports similar to how biomedical researchers describe their research methodologies by including the type and model of key instruments used in their experiments.
- On page 3 of the draft report it is stated that "Though no studies have been performed using add-back therapy for elagolix, it may be expected that such therapy would be considered for long-term use of higher doses of elagolix that result in full ovarian suppression." However, later in the report it notes that studies of elagolix with add-back therapy are ongoing for patients with endometriosis, as well as for women with uterine fibroids and heavy menstrual bleeding – and this information is also available at ClinicalTrials.gov.[xx] Therefore, the sentence on page 3 should be edited to clarify the existence of the ongoing research.
- The draft report's cost-effectiveness analyses are presented separately for two different clinical indications – including threshold price calculations in Table 4.15 and 4.16 on page 56. However, this implies that there exists a platform for indication specific pricing, which doesn't exist in the US – at least not for connected conditions such as dysmenorrhea and non-menstrual pelvic pain. We would appreciate it if ICER clarified its thinking behind – or the utility for – the draft report's bifurcated analysis and section of the report.

Conclusions & Recommendations

Patients Rising Now believes that ICER's draft report does not reflect the quality of life, productivity, and complexity of diagnosis and treatments that women with endometriosis actually face. Without adequately incorporating patients' voices into the process of defining and assessing the value of their treatment options, ICER's draft report creates a warped view of a complex situation, and may perpetuate biases and inequities in diagnosis, treatment, regulations, payment, and R&D efforts.

We recommend that ICER more fully address the range of real-world costs endometriosis has for women and their families – particularly the costs of personal and workplace productivity. We also recommend that ICER continue to assess and examine its methodology and perspectives for its work.

Sincerely,

Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

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[i] ICER May 2018 Draft Evidence Report ""Elagolix for Treating Endometriosis", p. 62

[ii] ICER May 2018 Draft Evidence Report ""Elagolix for Treating Endometriosis", p. 62

[iii] ICER May 2018 Draft Evidence Report ""Elagolix for Treating Endometriosis", p. 7

[iv] Quass, et al., "On-label and off-label drug use in the treatment of endometriosis", Fertility and Sterility, Vol. 103 (3), March 2015

[v] Ibid.

[vi] Hirsch, et al., "Diagnosis and management of endometriosis: a systematic review of international and national guidelines," BJOG 2018;125:556–564 (Published Online 27 November 2017)

[vii] Soliman, et al., "The Effect of Endometriosis Symptoms on Absenteeism and Presenteeism in the Workplace and at Home", J Manag Care Spec Pharm. 23(7):745-54, July 2017

[viii] https://www.bls.gov/news.release/pdf/ecec.pdf, https://www.bls.gov/news.release/ecec.nr0.htm

[ix] Soliman 2017, op. cit.

[x] Nnoaham, et al., "Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries", Fertility and Sterility, Vol. 96, No. 2, August 2011

[xi] Soliman 2017, op. cit.

[xii] ICER May 2018 Draft Evidence Report ""Elagolix for Treating Endometriosis", p. 38

[xiii] ICER May 2018 Draft Evidence Report ""Elagolix for Treating Endometriosis", p. 56

[xiv] ICER May 2018 Draft Evidence Report ""Elagolix for Treating Endometriosis", p. 50 and https://seekingalpha.com/article/4109208-abbvie-obtain-fda-approval-elagolix

[xv] ICER May 2018 Draft Evidence Report ""Elagolix for Treating Endometriosis", p. 46

[xvi] ICER May 2018 Draft Evidence Report ""Elagolix for Treating Endometriosis", p. 56

[xvii] http://www.businessinsider.com/irregardless-real-word-regardless-kory-stamper-education-dictionary-mean-girls-lexicon-merriam-webster-2017-6

[xviii] http://www.bbc.com/news/magazine-22223190

[xix] https://softwareengineering.stackexchange.com/questions/34120/how-often-do-cpus-make-calculation-errors

[xx] ICER May 2018 Draft Evidence Report ""Elagolix for Treating Endometriosis", p. 63 and https://clinicaltrials.gov/ct2/results?recrs=&cond=&term=Elagolix

May 31, 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

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.

1025 Connecticut Ave NW, Suite 601
Washington, DC 20036

T 202.223.8224
F 202.833.3472

W swhr.org

Society for Women's Health Research

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]

Society for Women's Health Research

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

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.