October 8, 2019

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

Dear Dr. Pearson,

On behalf of the Partnership to Improve Patient Care (PIPC), we are writing to provide comments on the Institute for Clinical and Economic Review's (ICER) draft evidence report on treatments for Type 2 Diabetes. 1.5 million Americans are diagnosed with diabetes each year, and it is the seventh leading cause of death in the United States.[1] Given these alarming statistics, it is vitally important we find effective treatments for diabetes patients and that evaluations of these treatments are conducted in a scientifically sound, patient-centric manner. Unfortunately, ICER's report contains significant methodological flaws: it continues to omit quality of life data patients deem valuable; uses a flawed data set that underestimates risk, burden, and treatment effect; and uses negative utilities, which imply there are health states worse than death.

We would like to highlight the following concerns with ICER's report:

ICER Continues to Omit Quality of Life Data Deemed Valuable by Patients, Instead Relying on Faulty Data That Claims Health States Worse Than Death

In this report, as in previous reports, ICER assumes the only impact a new therapy has on quality of life are movement between specific, clinical health states. In reality, there is a growing body of evidence that successful treatment of cardiovascular disease risk factors in patients, including those suffering from diabetes, have had strong effects on psychological wellbeing and quality of life beyond gains associated purely with their event risk effects or movements across health states.

For example, a recent study in long-term statin users showed lower depression, anxiety, and hostility after adjustment for the propensity for statin use and potential confounders. The beneficial psychological effects of the statins appeared to be independent of the drugs' cholesterol-lowering effects.[2] Similar results have been seen in drugs used to treat high blood pressure.[3]

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[1] American Diabetes Association. Statistics About Diabetes. Accessed September 18, 2019.
[2] Young-Xu Y, Chan KA, Liao JK, Ravid S, Blatt CM. Long-term statin use and psychological well-being. Journal of the American College of Cardiology. 2003 Aug 20;42(4):690-7.
[3] Croog SH, Levine S, Testa MA, Brown B, Bulpitt CJ, Jenkins CD, Klerman GL, Williams GH. The effects of antihypertensive therapy on the quality of life. New England Journal of Medicine. 1986 Jun 26;314(26):1657-64.

We are especially concerned about ICER's use of utility data. It is unacceptable that ICER continues to use negative utility values, which imply there are health states worse than death. ICER has used negative utilities in previous reports and has been heavily criticized for it. The academic literature has also shown negative utilities to not really exist.[4] We cannot stress enough the ethical ramifications - and irrational consequences - of using such methods to attribute a value to treatments that may then be used by payers to determine whether to cover a new treatment.

We also take serious issue with the source of the utility data. The utilities used for baseline Type 2 Diabetes, and various complications of Type 2 Diabetes are the most significant drivers of variance in the model. The source of these weights is cross-walked from unrelated studies, rather than waiting for actual data from ongoing trials, bringing into question the longer-term validity of the base case results. ICER even goes on to state in its report that;

" ... Utility values for events modeled from the risk equations were drawn from two sources due to a lack of a single comprehensive source of health-related quality of life inputs. It is also important to point out that the two sources used different preference-weighted measures (EQ-5D and HUI3), and these two instruments are known to produce slightly different utility estimates". *(Page 73)*

It is difficult to understand how ICER can justify reporting findings based on this data and approach given what is stated above.

ICER Ignores the Heterogeneity of Type 2 Diabetes Patients

A glaring limitation of ICER's analysis is its reporting of a single ratio of cost effectiveness of oral semaglutide against each comparator. Theoretically, the shift to microsimulation models should give outputs on an infinite number of potential patient types, but instead of taking advantage of this, ICER has retained a base case that gives just one set of cost-effectiveness ratios.

Type 2 Diabetes is particularly difficult and sensitive to treat, given the complexity of co-morbidities. This means that prescribing and prognosis are particularly heterogeneous and specific to individual patients. ICER admits this itself when describing the model:

"The overarching limitation of this model is the complexity of T2DM, its large number of co-morbidities, and its patient-specific clinical management." (Page 72)

ICER also notes that the primary aim of the report will be to evaluate the new drug in four very specific subgroups:

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[4] Bernfort L, Gerdle B, Husberg M, Levin LÅ. People in states worse than dead according to the EQ-5D UK value set: would they rather be dead?. Quality of Life Research. 2018 Jul 1;27(7):1827-33.

1. Patients at high risk for CV events
2. Patients with moderate-to-severe renal impairment
3. Patients requiring a second antihyperglycemic agent (i.e., second-line therapy)
4. Patients requiring a third antihyperglycemic agent (i.e., third-line therapy)

Despite this nod to the fact that patients are heterogeneous and react differently to different treatments, there are no more references to these essential subgroup classifications in the section on cost-effectiveness. This exemplifies ICER's tendency to oversimplify and its unwillingness to accept that it is impossible to determine whether a treatment is "cost-effective" for the general population when patients are heterogenous with different comorbidities and treatment needs.

Healthcare is becoming more and more complex, and more and more specific to individuals with particular sets of diseases, complications, and co-morbidities. A continued reliance on a population perspective in reporting value statements is likely to become more and more misguided[5] and less and less beneficial to decision makers.[6, 7]

ICER Again Uses Artificially Narrow Definition of Major Adverse Cardiovascular Event

As in ICER's assessment of treatments for cardiovascular disease, ICER chooses to use an incredibly narrow definition of Major Adverse Cardiovascular Event (MACE). The definition of MACE in the base case is a shorthand version including only MI, stroke, and CVD death. More common and more comprehensive definitions of MACE include revascularizations and other events such as severe angina and heart failure.

Exactly how MACE is defined and what events are included is known to have a significant impact on outcomes.[8] It is concerning that, with this knowledge, ICER selected a less comprehensive measure of MACE.

The Source of Risk Equations for Patient Underestimates Value of Therapies

The risk equations ICER has chosen to use may artificially underestimate the value of therapies.

[5] Kravitz RL, Duan N, Braslow J. Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. The Milbank Quarterly 2006; 84(4): 759.

[6] Basu A. Economics of individualization in comparative effectiveness research and a basis for a patient-centered healthcare. Journal of Health Economics 2011; 30(3): 549-559.

[7] Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA.* 2016;316(10):1093–1103.

[8] Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention. Journal of the American College of Cardiology. 2008 Feb 19;51(7):701-7.

The model used is based on data from a United Kingdom-based sample.[9] Metabolic syndrome conditions and diabetes itself are more prevalent in the population of the United States, so using a United Kingdom data set may underestimate risk of cardiovascular events in the population of need, hence underestimating absolute benefits from successful treatment.

It is also worth pointing out that the risk algorithms generated from the United Kingdom Prospective Diabetes Study (UKPDS) are less reliable generally, and for an American population specifically, than those generated more recently by the RECODe study using data from the Action to Control Cardiovascular Risk in Diabetes study (ACCORD; 2001–09).[10] Nevertheless, both sets of risk equations suffer from the fact they are generated on a very narrow selection of participants, as they rely on data from clinical trials rather than being taken from a real world population that is likely to be more representative of the actual population that could benefit from the treatment under investigation. A number of studies have highlighted the limitations of trial data only in generating risk equations for models that will ultimately make decisions about actual populations of need, and all suggest that both risk and event rates are underestimated as a result.[11, 12, 13]

ICER's Budget Impact Model Continues to be Concerning as it is Equivalent to Budget Capping in Health Care.

We continue to be concerned with ICER's problematic tactic of budget capping in healthcare. Following ICER's disturbing pattern, this report assumes that only a little over 4% of eligible patients could be treated with oral semaglutide in a given year without crossing ICER's arbitrary budget threshold.

As we described at length in our recent comments on cardiovascular disease, budget capping both presents a significant ethical problem and is also illogical. This concept tells us we can only give a new, effective drug to a certain number of people who could benefit from it. Since the goal of the healthcare system is ultimately better health, this premise does not make sense.

[9] Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia. 2013 Sep 1;56(9):1925-33.

[10] Basu S, Sussman JB, Berkowitz SA, Hayward RA, Yudkin JS. Development and validation of Risk Equations for Complications Of type 2 Diabetes (RECODe) using individual participant data from randomised trials. The Lancet Diabetes & Endocrinology. 2017 Oct 1;5(10):788-98.

[11] Franklin JM, Schneeweiss S. When and how can real world data analyses substitute for randomized controlled trials?. Clinical Pharmacology & Therapeutics. 2017 Dec;102(6):924-33.

[12] Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. European heart journal. 2015 Jan 13;36(19):1163-70.

[13] Finegold JA, Raphael CE, Levy WC, Whinnett Z, Francis DP. Quantification of survival gain from cardiac resynchronization therapy: nonlinear growth with time, and greater gain in low-risk patients, make raw trial data an underestimate of real-world behavior. Journal of the American College of Cardiology. 2013 Dec 24;62(25):2406-13.

The model itself is also not sound. ICER's budget impact model assumes a take-up rate of 100% over five years for these new drugs, which assumes that every single person that could theoretically benefit from these interventions will ultimately receive it. This is illogical and have been proven incorrect time and time again, yet ICER persists in making this assumption. A prime example of this is ICER's budget impact model for PCSK9i drugs in 2015.[14] That report also relied on the unrealistic assumption of full take-up over five years. Four years later the take-up rate of PCSK9 inhibitors is estimate at less than 1%.[15]

Conclusion

ICER continues to use a flawed methodology, ignoring the reality of heterogeneous patient populations and quality of life outcomes that matter to patients in favor of data that easily crosswalks into the discriminatory QALY metric. We urge ICER to consider alternative methodologies that will foster improved health care decisions for individual patients.

Sincerely,

Tony Coelho
Chairman, Partnership to Improve Patient Care

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[14] https://icer-review.org/wp-content/uploads/2016/01/Final-Report-for-Posting-11-24-15-1.pdf
[15] Chamberlain AM, Gong Y, Shaw KM, Bian J, Song WL, Linton MF, Fonseca V, Price-Haywood E, Guhl E, King JB, Shah RU. PCSK9 Inhibitor Use in the Real World: Data From the National Patient-Centered Research Network. Journal of the American Heart Association. 2019 May 7;8(9):e011246.