PIPC Partnership to Improve Patient Care

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Dear Ms. Emond,

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) assessment on chronic obstructive pulmonary disease (COPD).

COPD impacts almost 16 million Americans. It is a highly heterogeneous condition, which can make it challenging to treat.[1] Given this reality, it is important that ICER accurately capture the value of new treatments, as segments of the patient population still desperately need new options. We encourage ICER to consider the following comments.

ICER's sources of data do not accurately capture the reality for COPD patients in the United States.

ICER's choice of data for costs per exacerbation appear to underestimate the true cost of exacerbations in the United States. The ICER model uses a single study that found the cost of moderate exacerbation estimated at $2,415 and a severe exacerbation at $26,047. This study relies on a sample of 300,000 patients. A much larger recent study that utilized data from CMS[2] suggested a range of cost per exacerbation of between $26,544 - $43,774 based on category of severity. This data relied on a much larger sample size of just under four million patients. In this instance, the more recent study with a larger sample population appears to provide more credible data. We would suggest that, where available, ICER should be using the most recent and largest studies.

We are also concerned that the sources used for mortality modifiers by COPD severity may underestimate the years of life lost due to COPD. The ICER model assumes standardized mortality ratios compared to those without COPD as 1.3 for moderate, 1.6 for severe and 1.9 for very severe.[3] The original source is a European study using Eurostat data from 21 countries, and states that the measures of severity varied widely by country. The paper itself is a request to improve standardization of outcome measures in COPD. There is a better source for mortality

[1] https://www.copdfoundation.org/What-is-COPD/Understanding-COPD/What-is-COPD.aspx
[2] Sethi S, Make BJ, Robinson SB, Kumar S, Pollack M, Moretz C, Dreyfus J, Xi A, Powell D, Feigler N. Relationship of COPD exacerbation severity and frequency on risks for future events and economic burden in the medicare fee-for-service population. International Journal of Chronic Obstructive Pulmonary Disease. 2022 Mar 20:593-608.
[3] Atsou K, Chouaid C, Hejblum G. Variability of the chronic obstructive pulmonary disease key epidemiological data in Europe: systematic review. BMC medicine. 2011 Dec;9:1-6.

ratios that is based on United States data.[4] This study estimates standardized mortality ratios compared to those without COPD as 1.6 for moderate COPD and 2.7 for severe COPD. As ICER's assessments are conducted for an American audience and meant to drive decision making within the United States health care system, the paper based on United States data would be the more accurate source.

Finally, ICER's health state utility values are derived from a randomized clinical trial when real world data is available and more accurate. ICER uses utility scores of 0.787 for moderate, 0.750 for severe and 0.647 for very severe COPD. These are second hand and taken from a multi-center randomized clinical trial (RCT) using the UK value set[5]. Over the years, PIPC has laid out the many limitations that result from using utility data derived solely from the trial setting. RCT populations are generally much healthier than real-world disease-specific populations.[6] There are always explicit and implicit exclusion criteria for recruitment into trial settings,[7] including age, the existence of co-morbidities[8] and levels of healthcare access and utilization, that make RCT populations rarely representative of real-world populations of need.[9, 10]

In addition, utilities in RCTs tend to be inflated compared to non-RCT samples of patients[11] as EQ5D gains are often generated for patients in RCTs that are non-disease or treatment related socio-emotive components, that can occur because of receiving greater care and attention from healthcare professionals. There is also a placebo effect from patients in both arms of the trial. Numerous studies have highlighted the utilities generated in RCTs are generally much higher than the equivalents would be for a real-world population.[12]

Ultimately, ICER should be looking to use the best possible sources that are most representative of the population in need of treatment. This should include prioritizing sources based on United States data, large sample sizes, real-world data, and the most recent publications.

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[4] Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. Thorax 2003 May; 58(5):388–393.
[5] Rutten-van Mölken MP, Oostenbrink JB, Tashkin DP, Burkhart D, Monz BU. Does quality of life of COPD patients as measured by the generic EuroQol five-dimension questionnaire differentiate between COPD severity stages?. Chest. 2006 Oct 1;130(4):1117-28.
[6] Mitchell AP, Harrison MR, Walker MS, George DJ, Abernethy AP, Hirsch BR. Clinical trial participants with metastatic renal cell carcinoma differ from patients treated in real-world practice. Journal of oncology practice. 2015 Nov;11(6):491-7.
[7] Knepper, T.C. & McLeod, H.L. When will clinical trials finally reflect diversity? *Nature* **557**, 157–159 (2018).
[8] Unger, J.M., Hershman, D.L., Fleury, M.E. & Vaidya, R. Association of patient comorbid conditions with cancer clinical trial participation. *JAMA Oncol*. **5**, 326 (2019).
[9] Mishkin, G., Arnaldez, F. & Percy Ivy, S. Drivers of clinical trial participation—demographics, disparities, and eligibility criteria. *JAMA Oncol.* **5**, 305–306 (2019).
[10] Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. Trials. 2015 Dec;16(1):1-4.
[11] Bradburn MJ, Lee EC, White DA, Hind D, Waugh NR, Cooke DD, Hopkins D, Mansell P, Heller SR. Treatment effects may remain the same even when trial participants differed from the target population. Journal of Clinical Epidemiology. 2020 Aug 1;124:126-38.
[12] Villines TC, Cziraky MJ, Amin AN. Awareness, knowledge, and utility of RCT data vs RWE: results from a survey of US cardiologists: real-world evidence in clinical decision making. Clinical Medicine Insights: Cardiology. 2020 Sep;14:1 179546820953410.

Evidence suggests that frequency of exacerbations is related to significantly worse survival outcomes, a dynamic that is not captured in ICER's model.

Exacerbations, whether treated or untreated, have a detrimental and prolonged impact on patients' health status and outcomes,[13,14] and have cumulative negative effects on lung function over time.[15] COPD exacerbations are highly heterogeneous, varying in severity and phenotype. Evidence has shown that exacerbations are related to worse survival outcomes,[16] yet the model only bases risk of mortality modifiers on severity level, not rate of exacerbations. The frequency of exacerbations is also a marker of both disease burden and mortality risk.[17] Frequent exacerbations, mainly in patients with severe COPD, accelerate disease progression and mortality.[18] This is a dynamic also ignored in the ICER model.

Exacerbations of COPD also have a cumulative effect on lung function. Patients in the 3-year TORCH study who experienced 0–1.0 moderate to severe exacerbations per year had a 37% faster decline in lung function than those with no exacerbations. Among those patients who experienced more than one moderate to severe exacerbation, the rate of decline in lung function was 65% faster.[3] Rate of exacerbations also varies strongly not just by severity but also by age and gender[19], the dynamic nature of which is not adequately represented using a single estimate of exacerbations per cycle used in the model.

The ICER model largely ignores the complexity of this dynamic between lung function and exacerbation rate over time, and the impact of exacerbation rate on mortality and disease progression. This is a stark omission, as it will not allow ICER's assessment to capture an accurate value of treatment of COPD.

ICER Continues to Use the Discriminatory QALY and the Similar Measure evLYG.

Multiple studies have shown that cost-effectiveness models using the quality-adjusted life year (QALY) discriminate against patients with chronic conditions, [20] like COPD, and people with disabilities.[21] There is widespread recognition that the use of the QALY is discriminatory,

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[13] Jones PW, Lamarca R, Chuecos F, Singh D, Agustí A, Bateman ED, de Miquel G, Caracta C, Gil EG. Characterisation and impact of reported and unreported exacerbations: results from ATTAIN. European Respiratory Journal. 2014 Nov 1;44(5):1156-65.
[14] Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax. 2012 Nov 1;67(11):957-63.
[15] Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW, Vestbo J, Knobil K, Yates JC, Calverley PM. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. American journal of respiratory and critical care medicine. 2008 Aug 15;178(4):332-8.
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[18] Anzueto A. Impact of exacerbations on COPD. European Respiratory Review. 2010 Jun 1;19(116):113-8.
[19] Oshagbemi OA, Keene SJ, Driessen JH, Jordan R, Wouters EF, de Boer A, de Vries F, Franssen FM. Trends in moderate and severe exacerbations among COPD patients in the UK from 2005 to 2013. Respiratory Medicine. 2018 Nov 1;144:1-6.
[20] Paulden M. Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable?. Expert review of pharmacoeconomics & outcomes research. 2017 May 4;17(3):239-42.
[21] Nord E, Pinto JL, Richardson J, Menzel P, Ubel P. Incorporating societal concerns for fairness in numerical valuations of health programmes. Health economics. 1999 Feb;8(1):25-39.

reflected in laws that bar its use in government decision-making. The National Council on Disability (NCD), an independent federal agency advising Congress and the administration on disability policy, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments.[22]

Additionally, we share the concerns of NCD about the equal value of life year gained (evLYG), a similar measure created by ICER to supplement the QALY. The evLYG is a simplistic fix attempting to address criticism that the QALY devalues life years lived with a disability, yet it fails to account for oversimplified measures of quality-of-life gains in expected life years (not extended life years) and it does not account for any health improvements in extended life years. Like the QALY, the evLYG relies on average estimates based on generic survey data and obscures important differences in patients' clinical needs and preferences, particularly those with complex diseases and from underrepresented communities.[23] It assumes that people value life year gains more than quality of life improvements, giving a lower value to health interventions in patient populations that have a lower life expectancy or fewer life years gained from treatment, which may include people with disabilities, underlying chronic conditions, the elderly, and certain communities of color.[24] With the evLYG and the QALY, ICER promotes two compromised and flawed measures of health gain. Deciding which to choose is confusing and inconsistent.

ICER fails to capture the heterogeneous nature of COPD.

As ICER notes in its report, COPD is a widely heterogenous disease[25] both in terms of the cause, the level of comorbidity,[26] and its impact on patient experience.[27] This points to a larger issue with respect to value assessment reporting is that the archetypal cost-effectiveness model relies heavily on producing effect size based on population averages, and rarely are results specific to subpopulations released in results.[28] It is well established that generating and reporting of

[22] https://www.ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf
[23] DiStefano MJ, Zemplenyi A, Anderson KE, Mendola ND, Nair KV, McQueen RB. Alternative approaches to measuring value: an update on innovative methods in the context of the United States Medicare drug price negotiation program. Expert Rev Pharmacoecon Outcomes Res. 2024 Feb;24(2):171-180. doi: 10.1080/14737167.2023.2283584. Epub 2024 Jan 25. PMID: 37961908.
[24] Mike Paulden, Chris Sampson, James F. O'Mahony, Eldon Spackman, Christopher McCabe, Jeff Round, Tristan Snowsill, Logical Inconsistencies in the Health Years in Total and Equal Value of Life-Years Gained, Value in Health, Volume 27, Issue 3, 2024, Pages 356-366.
[25] Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, MacNee W, Miller BE, Rennard S, Silverman EK, Tal-Singer R. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respiratory research. 2010 Dec;11:1-4.
[26] Vogelmeier CF, Chapman KR, Miravitlles M, Roche N, Vestbo J, Thach C, Banerji D, Fogel R, Patalano F, Olsson P, Kostikas K. Exacerbation heterogeneity in COPD: subgroup analyses from the FLAME study. International journal of chronic obstructive pulmonary disease. 2018 Apr 10:1125-34.
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[28] Lavelle TA, Kent DM, Lundquist CM, Thorat T, Cohen JT, Wong JB, Olchanski N, Neumann PJ. Patient variability seldom assessed in cost-effectiveness studies. Medical Decision Making 2018;38(4):487–94

differential value assessment across subgroups leads to substantial health gains, both through treatment selection and coverage.[29,30]

If ICER is to take seriously its role of informing health policy decision makers about the value of new therapies, it needs to move away from the assumption that all patients are the same. No patient is average, and it is essential that ICER moves to acknowledge this and incorporate analysis of subpopulations and produce ranges of value rather than relying on an archetypal patient.

Conclusion

PIPC urges ICER to reconsider both its data sources and modeling choices if it seeks to provide an accurate representation of value to patients with COPD. Where available, real-world evidence based on United States populations should be relied on in the model. ICER must also move away from using discriminatory metrics and the antiquated practice of looking at value to an "average" patient.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

[29] Basu A. Economics of individualization in comparative effectiveness research and a basis for a patient-centered health care. Journal of health economics. 2011 May 1;30(3):549-59.
[30] Espinoza MA, Manca A, Claxton K, Sculpher MJ. The value of heterogeneity for cost-effectiveness subgroup analysis: conceptual framework and application. Medical Decision Making. 2014 Nov;34(8):951-64.