PIPC Partnership to Improve Patient Care

May 10, 2022

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

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report on treatments for beta thalessemia. PIPC remains concerned about many of ICER's modeling choices and their impact across its studies and would encourage ICER to consider the following.

ICER continues to use the discriminatory Quality-Adjusted Life Year (QALY).

As PIPC has commented previously, the use of discriminatory metrics, including the QALY, is inappropriate and too often results in a discriminatory impact. It is acknowledged that QALYs discriminate by design against people with disabilities and chronic illnesses.[1] There should be no room for discrimination in health care decision making, and we urge ICER to cease use of discriminatory metrics.

ICER's Model Takes a Narrow Perspective

The narrow perspective of ICER's model ignores the wider benefit of reduced demand on scarce health care resources, which overlooks a valuable facet of successful treatment of transfusion dependent beta thalassemia (TDBT).

TDBT patients account for a larger percentage of blood transfusions around the world. TDBT patients make up almost 18% of all blood transfusions in Greece,[2] and almost 10% in Hong Kong.[3] This is expected to rise to 30% by 2024. In the United Kingdom it is expected that the demand for blood products for TDBT patients is likely to rise by 20% in the next five years.[4] The European Committee on Blood Transfusion reported that most of the 45 countries evaluated had a nationally coordinated blood program (85%), but 25% of countries, including many countries with a high prevalence of hemoglobinopathies such as BT could not meet their national need for blood supplies.[5]

[1] https://ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf
[2] Politis C. Haemoglobinopathies: genetic and clinical aspects with an impact on blood transfusion. ISBT Science Series. 2013 Jun;8(1):229-32.
[3] Au WY, Lee V, Lau CW, Yau J, Chan D, Chan EY, Cheung WW, Ha SY, Kho B, Lee CY, Li RC. A synopsis of current care of thalassaemia major patients in Hong Kong. Hong Kong Med J. 2011 Aug 1;17(4):261-6.
[4] Currie CJ, Patel TC, McEwan P, Dixon S. Evaluation of the future supply and demand for blood products in the United Kingdom National Health Service. Transfusion Medicine. 2004 Feb;14(1):19-24.
[5] European Directorate for the Quality of Medicines & HealthCare Report of the survey on blood supply management Available from: www.edqm.eu/medias/fichiers/report_survey_on_blood_supply_management_2012.pdf, Accessed 15th April 2022

The red blood cells required for blood transfusions are a finite resource. Given this reality, the successful treatment of people living with TDBT would lead to benefit for patients with other blood disorders, as it would be less likely they would face shortages of necessary red blood cells. This system wide value gain is not incorporated into standard cost-effectiveness modeling, and this narrow perspective ignores the effects of redistribution of scarce natural resources. It is not unprecedented to construct a model that captures a treatment's broader impact on the health care system. There have been studies evaluating the wider public health value of successful treatment of hepatitis C and the resulting impact on the freeing up of essential organs for transplant and the resulting health gain to patients with conditions other than hepatitis C in the healthcare system.[6, 7] To fully capture the societal value of gene therapy in TDBT, economic models should also capture the value of reduced supply-demand shortfall for blood products in the healthcare system and the lives saved as a result.

ICER uses a Decision-Tree Markov Model to Estimate Cost-Effectiveness, Whereas a Time-To-Event Methodology Would Be a More Appropriate Mechanism.

ICER's model is centered on transfusion dependence: how often transfusions were required and how long a patient went without needing a transfusion. Given this desired outcome, the most effective model for comparing two scenarios (with and without gene therapy in this example) would be a time-to-event methodology such as a discrete event simulation model (DES)[8],[9] or a discretely integrated condition event (DICE) model.[10,11]

The one published economic evaluation of gene therapy treatment in beta thalassemia used a DICE methodology and uses largely the same sets of inputs as the ICER model but its conclusion was that Beti-cel was much more cost-effective than that estimated by the ICER model. These methods also allow for the integration of a wider set out of outcomes of interest throughout the course of the disease and the lifetime of the patient being simulated, which would help alleviate the problem with the ICER model's overly limited concentration on one aspect of the patient journey, transfusion dependence.

The mortality ratio for transfusion dependent beta thalassemia used in the model is at the low end of recent estimates.

The model developed uses 3.5 as an estimate of the standardized mortality ratio (SMR) for transfusion dependent patients – or patients in periods of transfusion dependence. Other estimates of the SMR in the

[6] Jena AB, Stevens W, Gonzalez YS, Marx SE, Juday T, Lakdawalla DN, Philipson TJ. The wider public health value of HCV treatment accrued by liver transplant recipients. The American journal of managed care. 2016 May;22(6 Spec No.):SP212-9.
[7] Jena AB, Snider JT, Espinosa OD, Ingram A, Gonzalez YS, Lakdawalla D. How does treating chronic hepatitis C affect individuals in need of organ transplants in the United Kingdom?. Value in Health. 2019 Jun 1;22(6):669-76.
[8] Standfield L, Comans T, Scuffham P. Markov modeling and discrete event simulation in health care: a systematic comparison. International journal of technology assessment in health care. 2014 Apr;30(2):165-72.
[9] Getsios D, Blume S, Ishak KJ, Maclaine G, Hernández L. An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom. Alzheimer's & Dementia. 2012 Jan 1;8(1):22-30.
[10] Moller J, Davis S, Stevenson M, et al. Validation of a DICE simulation against a discrete event simulation implemented entirely in code. Pharmacoeconomics. 2017;35(10):1103–1109.
[11] Caro JJ. Discretely integrated condition event (DICE) simulation for pharmaco-economics. Pharmacoeconomics. 2016;34(7):665–672.

literature range from 6.2[12] to 13.5.[13] This likely means that the value of reducing need for transfusions and the reduction of patients in the transfusion-dependent states would have a much higher mortality impact than is currently reported in the draft ICER report.

The number of transfusions used in the model is likely low.

ICER's model assumes that patients under 18 years of age have an average of 14.95 transfusions per year, and patients 18 years of age or older have an average of 16.1 transfusions per year, which is based on MarketScan data reported in Kansal 2021. Other studies suggest this might be an underestimate of the burden of TDBT. Recent studies suggest 17-41 transfusions per year.[14,15] It is essential that ICER's model accurately reflect the patient experience, so we would encourage ICER to revisit these inputs to assure it is captured correctly.

Conclusion

We continue to encourage ICER to reevaluate its modeling choices, particularly the use of the discriminatory QALY, in future studies. We hope that our comments are useful to ICER in developing its final evidence report.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

[12] Jobanputra M, Paramore C, Laird SG, McGahan M, Telfer P. Co-morbidities and mortality associated with transfusion-dependent beta-thalassaemia in patients in England: a 10-year retrospective cohort analysis. British Journal of Haematology. 2020 Dec;191(5):897-905.
[13] Ladis V, Chouliaras G, Berdoukas V, Chatziliami A, Fragodimitri C, Karabatsos F, Youssef J, Kattamis A, Karagiorga-Lagana M. Survival in a large cohort of Greek patients with transfusion-dependent beta thalassaemia and mortality ratios compared to the general population. European journal of haematology. 2011 Apr;86(4):332-8.
[14] Sheth S, Weiss M, Parisi M, Ni Q. Clinical and economic burden of transfusion-dependent β-thalassemia in adult patients in the United States. Blood. 2017 Dec 8;130:2095.
[15] Alshamsi S, Hamidi S, Narci HO. Healthcare resource utilization and direct costs of transfusion-dependent thalassemia patients in Dubai, United Arab Emirates: a retrospective cost-of-illness study. BMC health services research. 2022 Dec;22(1):1-7.