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 thalassemia. 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
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


literature range from 6.2\textsuperscript{12} to 13.5.\textsuperscript{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.\textsuperscript{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,

\[ \underline{Coelho} \]

Tony Coelho
Chairman
Partnership to Improve Patient Care


