PIPC Partnership to Improve Patient Care

January 9, 2023

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 the opportunity to comment on the Institute for Clinical and Economic Review (ICER) assessment of Iptacopan and Danicopan for Paroxysmal Nocturnal Hemoglobinuria.

PNH is a rare blood disease, causing red blood cells to break apart because the surface of a person's blood cells is missing a protein that protects them from the body's immune system. As a result, hemoglobin is released. Experts estimate between 400 and 500 cases of PNH are diagnosed in the U.S. each year.[1] The condition presents burdens on patients related to travel, pregnancy and risks related to illness and surgery.[2] Therefore, it is imperative for ICER to directly engage with patients to understand their real-world experiences with the disease and its impact on their lives, as well as their clinicians managing the disease and adverse events. As you have heard from patients, there is a significant need for more treatment options for PNH patients and equitable access to those options.

As ICER conducts its assessment of treatments for PNH, PIPC urges it to consider the following comments related to its model.

ICER's choice of model underestimates the complexity of PNH and ignores major aspects of disease burden.

As PIPC has pointed out in the past, ICER tends to oversimplify models, which can frequently lead to assessments that do not account for the true burden of disease. ICER's PNH model is a simple three-state model that relies heavily on whether the PNH patient has reached a specific level of released hemoglobin, and subsequently whether that patient becomes transfusion dependent. This is an oversimplification of a complex condition.

Chronic anemia, fatigue, and the need for transfusion are common outcomes for patients with PNH. Yet, chronic anemia and fatigue are not incorporated into the ICER model. Including them would present a more holistic picture of the patient experience and improvement with treatment. Transfusion is included, but without significant regard for variance between the treatment arms, so the model is not able to present an accurate picture of the disease and potential treatment effects. The longer-term impacts of transfusion dependence and iron overload are also ignored by the model, which is a source of

[1] https://www.aamds.org/diseases/pnh
[2] https://www.aamds.org/diseases/pnh

considerable burden to PNH patients.[3] Transfusion dependence has a negative effect on a patient's quality of life and also requires substantial resources, including hospital admissions.[4] Spending some time to more thoroughly include these factors in the model would have presented both a more representative picture of patient improvement and potential cost savings related to treatment.

ICER should rely more heavily on real world evidence.

ICER has derived utility data from RCT data but could have chosen to run scenarios using utilities from real world studies or PNH cohorts. There are numerous reasons for preferring real-world cohort-based estimates of utilities, as clinical trials are renowned for recruiting "healthier" patients than those people who make up the real-world population of need.[5,6] It is also well known that trials tend to include a placebo effect on patients in the comparator arm.[7,8] In addition, patients in RCTs tend to receive far more non-treatment specific care and attention; symptom management interaction with clinicians and other medical staff, than the average patient in a real world setting.[9] As such quality of life measures in patients' non-response states are often higher for patient in RCTs than in real world cohort studies. Given this reality, relying on RCT data for utilities does not provide an accurate picture of the quality of life of the holistic patient population. To gain a more comprehensive understanding of improvement with treatment, ICER would do better to rely on real world evidence as the basis for its models.

ICER should make more of an effort to address patient heterogeneity.

PNH is a clinically heterogeneous disease. For example, for some patients, disease progression is characterized by florid intravascular, complement-mediated hemolysis, whereas in others, bone marrow failure dominates the clinical picture with modest or even no evidence of hemolysis observed.[10]

If the purpose of ICER is to provide insight into decision-making around the value of any new therapy for patients, it needs to produce an estimate – or a range of estimates – for as many of that wide range of patients, or patient types, as is possible. ICER's current model does not do this. Instead, ICER defers to the "average patient." This does not provide useful information on value that reflects a diverse

[3] McKinley C, Richards S, Munir T, et al. Extravascular hemolysis due to C3-loading in patients with PNH treated with eculizumab: defining the clinical syndrome. *Blood*. 2017;130(Suppl 1):3471.
[4] Platzbecker U, Hofbauer LC, Ehninger G, Holig K. The clinical, quality of life, and economic consequences of chronic anemia and transfusion support in patients with myelodysplastic syndromes. *Leuk Res*. 2012;36(5):525-36.
[5] Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, Dieppe P. The causes and effects of socio-demographic exclusions from clinical trials. Health Technology Assessment (Winchester, England). 2005;9(38):iii-152.
[6] Shrier I, Boivin JF, Steele RJ, Platt RW, Furlan A, Kakuma R, Brophy J, Rossignol M. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. American journal of epidemiology. 2007 Nov 15;166(10):1203-9.
[7] Hussain-Gambles M, Atkin K, Leese B. Why ethnic minority groups are under-represented in clinical trials: a review of the literature. Health & social care in the community. 2004 Sep;12(5):382-8.
[8] Glasziou PP, Simes RJ, Gelber RD. Quality adjusted survival analysis. Statistics in medicine. 1990 Nov;9(11):1259-76.
[9] West J, Wright J, Tuffnell D, Jankowicz D, West R. Do clinical trials improve quality of care? A comparison of clinical processes and outcomes in patients in a clinical trial and similar patients outside a trial where both groups are managed according to a strict protocol. BMJ Quality & Safety. 2005 Jun 1;14(3):175-8.
[10] Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. Hematology 2014, the American Society of Hematology Education Program Book. 2016 Dec 2;2016(1):208-16.

population. It is well established that generating and reporting of differential value assessment estimates across subgroups leads to substantial health gains, both through treatment selection and coverage.[11,12] If ICER seeks to develop reports that provide actionable and reliable information to health policy decision makers about the value of new therapies, it needs to move away from the assumption that all patients are average – an important step toward health equity.

ICER's model does not account for the true cost of PNH.

As PIPC has commented to ICER in the past, ICER's assessments would be more credible and more accurately depict value if they incorporated full societal costs and not just costs to the health care system. That being said, this model omits even some obvious costs to the health care system. Specifically, the model appears to capture only treatment cost and transfusion cost data. This does not paint a full picture, as patients with PNH will have many interactions with the healthcare system, in both inpatient and outpatient clinical settings, alongside the transfusion costs.

The paper that the ICER model references for its unit cost for transfusions[13] clearly states that the cost of transfusions is just a tiny fraction of overall healthcare costs associated with PNH. In this study it was estimated that a transfusion-dependent PNH patient's transfusion costs make up just $30,000 of an annual mean of $409,000 per year, the bulk of which are made up from outpatient visits and inpatient costs of $190,000 and $170,000 respectively. The paper suggests that a transfusion-dependent PNH patient may have total annual healthcare costs in the region of $409,000 as compared to a transfusion-free PNH patient of around $190,000. As both Iptacopan and Danicopan show rates of transition to transfusion dependent state at just a fraction (5-27%) of that in the ravulizumab arm (0.036 compared to 0.739 – 5%; 0.167 compared to 0.619; 27%), this would be a meaningful input.

Despite this data, ICER's model does not capture the savings of patients being on a drug that reduces the annual rate of a patient moving from a state that costs $200,000 per year to a state that costs $400,000 per year. Instead, it shows each patient having comparable annual "non-drug" costs over five years and that total "non-drug" cost is a maximum of $104,000 over five years. These numbers do not reflect the research ICER cites. PIPC urges ICER to take a closer look at its inputs and ensure it is capturing the full value of the treatments in question.

Conclusion

PIPC urges ICER to consider models that do not rely on quality-adjusted life years or equal value of life year gained measures in its studies. A model that allows for consideration of the complexity of a disease, the impact of treatment for different subpopulations, and the broader set of costs and savings for

[11] 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.
[12] 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.
[13] Cheng WY, Sarda SP, Mody-Patel N, Krishnan S, Yenikomshian M, Mahendran M, Lejeune D, Yu LH, Duh MS. Real-world healthcare resource utilization (HRU) and costs of patients with paroxysmal nocturnal hemoglobinuria (PNH) receiving eculizumab in a US population. Advances in Therapy. 2021 Aug;38:4461-79.

patients, medical and non-medical, would allow for a more accurate value assessment. We look forward to ICER's consideration of our comments in the final report and

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care