Tuesday, May 9th, 2023

Institute for Clinical and Economic Review
Two Liberty Square Boston, MA 02109
RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear Dr. Pearson,

We appreciate the opportunity to offer comments in response to the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report on Gene Therapies for Sickle Cell Disease (SCD). Our organizations represent the individuals most affected by your report - the patients and caregivers impacted by SCD and the community leaders who advocate for the SCD community.

Our comments will focus on key issues identified across the report and include recommendations to incorporate community perspectives into the revised report. The decisions you make in your report bear significant consequences — impacting coverage, access, out-of-pocket expenses, and many other outcomes. It is critically important for ICER to be thoughtful and deliberate in how it incorporates community input into the development of the economic modeling to ensure the analysis aligns with ICER's mission of amplifying the patient voice and supporting health equity in health technology assessments.

Our recommendations below center on the following key issues:

- Missing Data and the Premature Nature of the Review
- Urgent Need for Treatment Options
- Value and Efficacy Not Centered on Patient Experience and Perspective
- Incorrect Assumption of Annual VOCs
- Patient-Important Cost Not Included in the Base-Case Analysis
- Omission of Disease-Modifying Treatments in Costs and Definition of Standard Care

Missing Data and the Premature Nature of the Review

Racism has heavily affected the health care and outcomes of the SCD population since the clinical discovery of the disorder. For a century, the SCD community has been underfunded and devalued in research, innovation, and quality of care.[3] We would like to thank ICER for your work to listen to our patient community and appreciate how the "Background" section captures many realities of living with the disease.

Yet, your report does not account for the complexity of these issues and the larger implications they have on the rigor and accuracy of your cost-effectiveness conclusions. ICER has chosen to proceed with modeling and valuation despite known limitations in evidence and clear input from

concerned stakeholders about the equity implications of the premature nature of this review. Missing data is extremely problematic and will likely result in important unintended consequences. Given the concern that these other factors could easily confound your analyses, **we recommend ICER postpone this review until appropriate clinical evidence and real-world data are available.** If this is not possible, we expect ICER to provide justification and describe this within the "Uncertainty and Controversies" section in the final report.

Urgent Need for Treatment Options

Current treatments and models of care do not adequately address the complex challenges of SCD, which accounts for insurers paying $1.7 million on average for each person living with SCD.[4] These circumstances call for radical changes in the paradigm and practices of SCD care, including improving standards of clinician training, developing new research methods, and improving access and delivery of treatments. Because of its position in the U.S. health care field and its commitment to improve fair access across health insurance payer organizations, ICER is strategically positioned to make important contributions that will shape the future of SCD across the country. ICER's existing methods of cost-effectiveness analysis fail to adequately address this urgent need for treatments. **We recommend ICER incorporate these other potential benefits into the economic modeling used in this report.** If this is not possible, we expect ICER to provide justification and describe this limitation within the "Uncertainty and Controversies" section in the final report.

Value and Efficacy not Centered on Patient Experience and Perspective

Currently, there is wide variation in the definitions and metrics used as primary outcomes for SCD, and most notably, a misalignment between what is measured and what matters most to patients and their families. We applaud ICER for the inclusion of the list of patient-important outcomes, which highlights the patient-important short- and long-term outcomes and other related implications of SCD. However, modeling treatment effectiveness by using a primary measure of reduction in vaso-occlusive crisis (VOCs) perpetuates the aforementioned issue, as this is not centered on patient experience and perspective. Treatment success in the context of value assessment for gene therapy should be defined by the following patient-prioritized outcomes: improvement in health-related quality of life, improvement in emotional and mental health, reduction of the length and frequency of pain crises managed at home and medical setting, reduction in daily chronic pain, reduction in economic and financial burden, improvement in ability to age, reduction of fatigue, improvement in cognitive health and symptoms of mental fog, and reduction to the risk of organ damage and stroke. **We recommend ICER update the definition of treatment effectiveness and adjust the cost-effectiveness model to incorporate these patient-prioritized impacts as primary measures of efficacy.** If evidence is limited, ICER can work with patient groups to identify sources of evidence or to develop and administer surveys to get new data that can be used in the economic model. If this is

not possible, we expect ICER to include sensitivity analyses for each of these measures and describe this limitation within the "Uncertainty and Controversies" section in the final report.

Incorrect Assumption of Annual VOCs

There are noted differences between the definitions of severe SCD and vaso-occlusive crisis and events (VOCs and VOEs) used throughout this report, leading to confusion, inconsistencies, and incorrect assumptions. These differences are summarized below:

- In the lovo-cel trial, severe SCD was defined by **four or more severe vaso-occlusive events requiring health care** in the two years prior to enrollment.
- In the exa-cel trial, severe SCD was defined by **two or more severe VOCs requiring health care** per year in the two years prior to enrollment.
- The population for ICER's economic evaluation is stated as patients living with severe SCD. Severe SCD is defined as having **a minimum of four severe VOCs** in each of the two prior years.
- Later, in ICER's key model assumptions and inputs the patients on standard care were assumed to have **an average of four VOCs per year** until death. This creates a discrepancy compared to the population definition.

ICER's sensitivity analyses demonstrate that, for both treatments, the annual number of VOCs is a major driver of cost effectiveness, which raises concerns about ICER inappropriately choosing your assumption for the number of annual VOCs and undervaluing these treatments. **We recommend ICER update key assumption and inputs in base-case analysis to be more align with definitions, published evidence, and real-world experience**, by:

- **Correcting the input for the number of annual VOCs that require health care use to six VOCs per year.** The 2020 "My Life With Sickle Cell" survey collected information on VOCs from 454 patients and caregivers. Survey results indicate that individuals with SCD experience an average of 6.1 VOCs requiring health care use per year. This comprehensive study highlights the need to accurately reflect annual VOCs, which are typically under-represented in research.[5]
- **Removing non-severe patients or individuals with three or fewer VOCs per year from the average input criteria.** These individuals should be excluded from the economic evaluation based on ICER's population definition of severe SCD, which requires a minimum of four severe VOCs annually.

If additional evidence is needed, ICER should work with patient groups to identify sources of evidence related to the annual number of VOCs or to develop and administer surveys to get new data that can be used as a model input.

Patient-Important Cost Not Included in the Base-Case Analysis

Many patient-important outcomes and costs—transportation costs, impact on educational achievement, and annual pain events treated outside the hospital system[6], for example—are

omitted from ICER's analysis entirely despite strong and repeated emphasis on their importance from the SCD community during both the 2020 ICER review and the current review. For example, emerging data shows that patients often manage additional pain events at home each year that are typically excluded from calculated averages of annual VOCs. These events can last for days or weeks, with the main reason they chose to manage their VOCs at home due to previous poor experience in hospitals or Emergency Departments.[2,5,7] The exclusion of these outcomes from the model effectively assumes that the impact of these outcomes on value is equal to zero, which perpetuates issues like stigma and patients' experiences of racism and poor quality treatment during pain events. **We recommend ICER incorporate these patient-important outcomes and costs into both the base-case analysis and modified societal perspective analysis in order to accurately demonstrate the significance and burden of this disease.**

Omission of Disease-Modifying Treatments in Costs and Definition of Standard Care
Standard of care (SOC) for SCD is difficult to define, as different subtypes and individuals suffer from different complications, and comprehensive care is not clearly defined or standardized. ICER's definition of SOC raises concerns due to the exclusion of FDA-approved disease-modifying treatments. Several new treatments that have been approved over the last few years and are currently used in practice to manage severe SCD, including Adakveo®, Endari™, and Oxbryta®. Payer coverage policies often move coverage into concordance with standard of care defined in ICER reports, thus raising concerns that ICER's omission of these treatments will enable further access barriers and lead to denied access for patients. **We recommend ICER accurately reflect all available disease-modifying therapies in the definition of standard of care and estimate standard care costs based on the proportion of patients on each therapy, frequency, dosage, and unit costs for all FDA-approved therapies for SCD.**

We hope that you consider these recommendations. Should you have any questions or if you would like to discuss these comments further, please reach out to Sick Cells at info@sickcells.org.

Sincerely,

Advancing Sickle Cell Advocacy Project, Inc.
Association For Prevention of Sickle Cell Anemia Harford, Cecil, Eastern Shore
Axis Advocacy
Bridging the Gap - Adult Sickle Cell Disease Foundation of Nevada
Cayenne Wellness Center
Dreamsickle Kids Foundation, Inc.
Foundation for Sickle Cell Disease Research
Hope in Affliction, L.L.C
Kids Conquering Sickle Cell Disease Foundation

Martin Center Sickle Cell Initiative
May5Foundation
Metropolitan Seattle Sickle Cell Task Force
MTS Sickle Cell Foundation
North Alabama Sickle Cell Foundation, Inc.
Scott Center for Observation Treatment and Transition
SiCAWRE L.L.C.
Sick Cells
Sickle Cell Advocates of Rochester
Sickle Cell Association (St. Louis, MO)
Sickle Cell Association of Hillsborough County
Sickle Cell Association of Kentuckiana
Sickle Cell Association of Texas, Marc Thomas Foundation
Sickle Cell Association of West Alabama, Inc.
Sickle Cell Coalition of Maryland
Sickle Cell Community Consortium
Sickle Cell Disease Association of America, Central Alabama
Sickle Cell Disease Association of America, Inc.
Sickle Cell Disease Association of America, Inc. Northwest Louisiana Chapter
Sickle Cell Disease Association of America, Michigan Chapter
Sickle Cell Disease Association of America, Philadelphia/ Delaware Valley Chapter
Sickle Cell Disease Association of America, St. Petersburg Chapter
Sickle Cell Disease Association of Florida, Inc.
Sickle Cell Disease Association of Illinois
Sickle Cell Foundation of Minnesota
Sickle Cell Reproductive Health Education Directive
Sickle Cell Thalassemia Patients Network
Supporters of Families with Sickle Cell Disease, Inc.
The Maryland Sickle Cell Disease Association (MSCDA)
The Sickle Cell Association of New Jersey
The Sickle Cell Foundation of Tennessee
TOVA Community Health
Unspoken Hero Society
Uriel E. Owens Sickle Cell Disease Association of the Midwest
Virginia Sickle Cell Network
William E. Proudford Sickle Cell Fund Inc.
#ThroughThePain Inc.

Citations

1. Bradt P, Spackman E, Synnott PG, Chapman R, Beinfeld M, Rind DM, Pearson SD. Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value. Institute for Clinical and Economic Review, January 23, 2020. https://icer.org/wp-content/uploads/2020/10/ICER_SCD_EvidenceReport_031220-FOR-PUBLICATION.pdf

2. Drahos J, Boateng-Kuffour A, Calvert M, et al. Health-Related Quality of Life, Disease Impacts, and Health Equity Concerns in Adults with Sickle Cell Disease with Recurrent Vaso-Occlusive Crises: Preliminary Results from a Global Longitudinal Survey. *Blood*. 2022;140(Supplement 1):1387-1388. doi: https://doi.org/10.1182/blood-2022-157818

3. Farooq F, Mogayzel PJ, Lanzkron S, Haywood C, Strouse JJ. Comparison of US Federal and Foundation Funding of Research for Sickle Cell Disease and Cystic Fibrosis and Factors Associated With Research Productivity. *JAMA Network Open*. 2020;3(3):e201737. Doi: https://doi.org/10.1001/jamanetworkopen.2020.1737

4. Johnson KM, Jiao B, Ramsey SD, Bender MA, Devine B, Basu A. Lifetime medical costs attributable to sickle cell disease among nonelderly individuals with commercial insurance. *Blood Advances*. Published online May 16, 2022. doi:https://doi.org/10.1182/bloodadvances.2021006281

5. Sick Cells. "My Life with Sickle Cell" Survey Results. Published online 2020. https://sickcells.org/wp-content/uploads/2022/08/SCDAA-Convention-2020_Presentation-Slides.pdf

6. Osunkwo I, Andemariam B, Minniti CP, et al. Impact of sickle cell disease on patients' daily lives, symptoms reported, and disease management strategies: Results from the international Sickle Cell World Assessment Survey (SWAY). *American Journal of Hematology*. 2021;96(4):404-417. doi:https://doi.org/10.1002/ajh.26063

7. Pittman, D. D., Hines, P. C., Beidler, D., Rybin, D., Frelinger, A. L., Michelson, A. D., Liu, K., Gao, X., White, J., Zaidi, A. U., Charnigo, R. J., & Callaghan, M. U. (2021). Evaluation of longitudinal pain study in sickle cell disease (ELIPSIS) by patient-reported outcomes, actigraphy, and biomarkers. *Blood*, *137*(15), 2010–2020. https://doi.org/10.1182/blood.2020006020