September 20, 2019

Institute for Clinical and Economic Review
Two Liberty Square
Boston, MA 02109

RE: Draft Scoping Document for the Treatment of Sickle Cell Disease

Dear Dr. Pearson,

Sick Cells is pleased to have the opportunity to submit comments in response to the Institute for Clinical and Economic Review's (ICER's) Draft Scoping Document on treatments for sickle cell disease (SCD). Sick Cells is a patient advocacy organization that aims to elevate the voices of the SCD community. We would like to offer the following suggestions to ICER for consideration.

ICER should consider waiting until more research and insights are available to inform an appropriate methodology for the assessment of treatments this orphan disease. If ICER decides to move forward with the timeline, the points below outline areas in the scoping document that are (1) unclear and (2) recommendations that ICER should consider in its review of SCD.

1. Current methodology does not consider how differences in health insurance status affect the ability to pay for and ultimately engage in health services. Further, health insurance status of SCD patients may also be related to pre-existing health conditions and the severity of disease. According to the 2017 U.S. Census, Blacks or African Americans and Latinx have the highest un insurance rates.
2. The ICER review does not appear to account for the heterogeneity in treatment options.
    a. SCD is debilitating, occurring in about one of every 365 Black or African American births and one out of every 16,300 Latinx American births. About one in every 13 Black or African American babies are born with the sickle cell trait.
    b. Some patients will experience more or less benefit from treatment than the averages reported from clinical trials. The majority of ICER's review will rely on pharmaceutical clinical trials. These averages are somewhat helpful, but subgroup analyses are needed, especially for diseases that disproportionately impact specific populations. If the clinical trials for Crizanlizumab and Voxelotor SCD are not adequately powered and weighted to account for the disproportionate number of people of color impacted by the disease, the field will be unable to determine if these new medications will be beneficial for those most impacted.
        i. We recommend the routine use of sensitivity analyses in modeling to explore heterogeneity of treatment effects and avoid an overreliance on methods based on averaged estimates. The accuracy of analyses that change the age distribution or are specific to the Black or African American population would bolster confidence that the estimates and model assumptions are correct.
        ii. ICER should consider adding qualitative data in the form of patient and provider interviews and a stakeholder survey to help inform the sensitivity analyses. These qualitative data along with the quantitative will help test the robustness of the model.
3. ICER should clarify how the review methodology uses usual care (hydroxyurea and transfusions) as the control group.

a. SCD is a syndrome of diseases. Therefore, treatment cannot be classified as "usual care." Treatment is based on clinical manifestations of the disease and its comorbidities. Defining usual care as hydroxyurea and transfusions is inappropriate and further reasoning why it may be more appropriate to review SCD at a later date.

4. Quality-adjusted life years (QALYs) have significant limitations including ethical considerations, methodological issues, theoretical assumptions, and context or disease specific considerations.
    a. QALYs analyses fail to account for non-health benefits and indirect costs. Non-health benefits and in-direct costs and in particular, societal benefits, such as a faster return to work, improved ability to act as caregiver, better school performance, burden on and costs of caregiving, mental health challenges, daily functioning, time accessing medical care, income loss, loss of productivity, insurance premiums, out of pocket expenses, changes to home and vehicle, assistive devices/equipment, and travel costs are not factored into QALY calculations despite being of potentially considerable importance to SCD and other rare diseases. If these data are unavailable, ICER should clearly define how sensitivity analysis will be performed. ICER can also use Work Productivity and Activity Impairment (WPAI) index for indirect costs.
    b. QALYs utility scores fail to account for a variety of additional health-related factors such as severity of the initial health state and disease prevalence.
    c. ICER should clarify the estimation of capital costs in computing hospital costs. Current estimates use what the hospital billed to the payee, not the patient. Other direct costs include emergency department visits and medications.
    d. QALYs analysis currently include a population average. However, SCD generally affects the very young and younger adults. Therefore, ICER should consider analysis using at least two different age groups that reflect the ages SCD typically affects 25% under age 18; 75% 18 years and older. Furthermore, there is an aging population of patients with SCD. It is unclear how the ICER review will address patients over age 45.
    e. The average population analysis of QALYs also does not account for Blacks and African Americans being disproportionately affected. It would be best to review averages within Black and African American populations.
    f. Current QALYs methodology does not account for the impact of those with fewer treatment options. QALYs gained could be considered alongside other quantified aspects of benefit and combined in a way that reflects the trade-offs people are willing to make between an aggregate measure of benefit considered alongside cost. For some patients, a modest, incremental gain may be clinically meaningful and may significantly improve quality or length of life. However, the QALYs analyses are not sensitive enough to measure small but clinically meaningful changes in health status or utility.
        i. QALYs could be 'weighted' to reflect any differences in the value society places on QALYs gains by some patients that is supported by patient preferences.
        ii. There are a set of methods available to facilitate understanding patient preferences known as multiple criteria decision analysis (MCDA) that could be used.
    g. Patients with lower QALYs, whose lives are extended, will have overall higher/unfavorable incremental cost per QALYs than patients with mild disease.
        i. Currently, it is unclear how the model will incorporate different disease states. The QALYs by disease state could vary considerably.

ii. It may be best to consider the review of SCD in two different disease state categories: (1) acute events and (2) chronic conditions. Each disease state has different medical interventions.

5. It is unclear how ICER will address multiple patient outcomes
    a. Possible suggestions are to use a health index by combining all the health outcomes with different weights
6. The ICER definition of serious health condition is unclear.
    a. The definition of serious condition should not be subjective but instead based on predefined criteria accepted by clinicians and patients.
    b. QALY estimates vary depending on the seriousness of the health condition. Therefore, it is important to clearly define serious health condition, and how to account for many comorbidities and side effects of medical interventions patients with SCD experience.
7. Highlight the limitations of non-randomized control trial (RCT) data sources.
    a. If ICER decides to incorporate additional sources of non-RCT data, limitations should be noted.
        i. Clearly defined outcomes such as survival time or analysis end points that are evaluated by ICER must be pre-specified by the researchers and not the result of secondary or tertiary post hoc analyses. These time considerations are not clearly defined in the protocol and it is important for ICER to consider a time long enough to capture all potential differences in costs and outcomes.
        ii. ICER should fully disclose all data sources and approaches that inform the contextual considerations sections of ICER reviews to provide increased transparency in the assessment process.
8. Considerations for the Markov model
    a. ICER should clarify the different disease states in the Markov model and how transitions between disease states will impact cost estimates.
    b. It is also important to perform a sensitivity analyses on the assumptions and parameters used in Markov model. Performing this step allows one to see how sensitive the results are to slight changes to parameter values.

Thank you for your consideration of these suggestions. Sick Cells will continue to engage with ICER throughout this review to ensure that the patient perspective is effectively heard and valued.

Sincerely,

Ashley Valentine, MRes

President and CEO

Adam et al., (2017). Depression, quality of life and medical resource utilization in sickle cell disease Blood Advances 2017 1:1983-1992.

Anderson et al., (2015). Fatigue in Children with Sickle Cell Disease: Association With Neurocognitive and Social-Emotional Functioning and Quality of Life. J Pediatr Hematol Oncol.

Artz,N., Whelan, C., and Feehan, S. (2010). Caring for the Adult With Sickle Cell Disease: Results of a Multidisciplinary Pilot Program. Journal of the National Medical Association, 102(11):1009-1016. Print.

Ballas, S. K. (2009). "The cost of health care for patients with sickle cell disease." Am J Hematol 84(6): 320-322.

Blinder, M. A., et al. (2013). "Age-related treatment patterns in sickle cell disease patients and the associated sickle cell complications and healthcare costs." Pediatr Blood Cancer 60(5): 828-835.

Bou-Maroun et al., (2017). An analysis of inpatient sickle cell disease: incidence, costs and outcomes. Journal of Children and Youth Services Review. 10(1016);84.

Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, et al. Effect of hydroxyureaon the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med. 1995 May 18;332(20):1317-22.

Connolly et al., (2019). Neurocognitive and psychological effects of persistent pain in pediatric sickle cell disease. Pediatr Blood Cancer. 66(9);27823.

Cronin et al., (2019). Risk factors for hospitalizations and readmissions among individuals with sickle cell disease: results of a U.S. survey study. Hematology. 24(1);189-198.

Derlega et al.(2014). How Patients' Self-Disclose about Sickle Cell Pain Episodes to Significant Others Relates to Living with Sickle Cell Disease *Pain. Medicine.15*(9); 1496–1507.

Fingar K. Ret atl., (2019). Characteristics of Inpatient Hospital Stays Involving Sickle Cell Disease, 2000–2016. HCUP Statistical Brief #251. Agency for Healthcare Research and Quality, Rockville, MD.

Freed, G. L. (2019). A Missed Opportunity to Address a National Shame: The Case of Sickle Cell Disease in the United States. JAMA Pediatr.

Gilbert SK. The health insurance plight of patients with sickle cell disease. J Natl Med Assoc. 1986;78(7):663–665.

Haywood, C., Tanabe P., Naik, R., et al. (2013). The Impact of Race and Disease on Sickle Cell Patient Wait Times in the Emergency Department. American Journal of Emergency Medicine, 31(4): 651-656.

Hilliard, D. (2008). "The Black Panther Party Service to the People Programs."

Kauf et al, (2009). The cost of healthcare for children and adults with sickle cell disease. Am J Hematol. Jun;84(6):323-7

Lanzkron, S., et al. (2006). "Hospitalization rates and costs of care of patients with sickle-cell anemia in the state of Maryland in the era of hydroxyurea." Am J Hematol 81(12): 927-932.

Lovett, P.b., Sule, H.P., and Lopes, B.L. (2014). Sickle Cell Disease in the Emergency Department. Emergency Medicine Clinics of North America, 32: 629-647. Print.

Madani et al., (2018). Quality of life among caregivers of sickle cell disease patients: a cross sectional study Health Qual Life Outcomes.16: 176.

Maitra, P., et al. (2017). "Risk factors for mortality in adult patients with sickle cell disease: a meta-analysis of studies in North America and Europe." Haematologica.

Mosaku et al., (2015). Avascular necrosis significantly impairs quality of life in sickle cell disease. J Clin Sci. 12(1); 41-47.

National Heart, Lung, and Blood Institute, National Institutes for Health. (2002). The Management of Sickle Cell Disease. 4th ed. NIH Publication, 02(2117): 59-74.

National Heart, Lung, and Blood Institute. (2014). Evidence-based Management of Sickle Cell Disease.

National Heart, Lung and Blood Institute, National Institutes for Health. (2015). What Are the Signs and Symptoms of Sickle Cell Disease.

Paulukonis, S., et al. (2016). "Defining Sickle Cell Disease Mortality Using a Population-Based Surveillance System, 2004 through 2008." Public Health Rep 131: 367-375.

Piel et al., (2017). Associations between environmental factors and hospital admissions for sickle cell disease. Haematologica. 102; 666-675.

Rantanwongsa, N., Haywood, C., Bediako, S.M., et.al. (2009). Health care provider attitudes toward patients with acute vaso-occlusive crisis due to sickle cell disease: development of a scare. Patient and Education Counseling, 27; 272-278.

Sickle cell disease. (2012). Genetics Home Reference, National Institutes of Heart Lung and Blood.

Sickle Cell Disease Guideline Panel. Sickle cell disease: screening, diagnosis, management, and counseling in newborns and infants. Clinical Practice Guideline No.6. Rockville, MD: Agency for Healthcare Policy and Research, U.S. Department of Health and Human Services, 1993 (AHCPR publication 93-0562).

Singh et al., (2014). Economic Impact of Sickle Cell Hospitalization. Blood, 124 (21):5971.

Solomon, L.R. (2008). Treatment and prevention of pain due to vaso-occlusive crisis in adults with sickle cell disease: an educational void. Blood; The American Society of Hematology, 111(3), 997-1003. Print.

Sonik et al., (2018). Unmet legal and social advocacy needs of children with sickle cell disease: implications for health care payer costs.

Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. JAMA. 2003 Apr 2;289(13):1645-51. Erratum in JAMA. 2003 Aug 13;290(6):756.

Tenabe, P. (2012). Adult Emergency Department Patients with Sickle Cell Pain Crisis: Results from a Quality Improvement Learning Collaborative Model to Improve Analgesic Management. Academy of Emergency Medicine, 19(4): 430-438. Print.

Umeh et al., (2017). The psychosocial impact of leg ulcers in patients with sickle cell disease: I don't want them to know my little secret. PLoS One. 12(10).

The Voice of the Patient: A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative. Public Meeting: February 7, 2014. Report Date: October 2014. White Oak, MD. U.S. Department of Food and Drug Administration, 2014.

Wakefield, E. O., et al. (2018). "Describing Perceived Racial Bias Among Youth With Sickle Cell Disease." J Pediatr Psychol.