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,

As key stakeholders in the sickle cell disease (SCD) community, we recommend you postpose the SCD review and reschedule the review for a later date. We agree with and understand the Institute for Clinical and Economic Review's (ICER) overarching mission to ensure SCD patients have access to effective and affordable treatments. After review of the Draft Scoping Document, we have concerns about ICER's ability to accurately evaluate Crizanlizumab and Voxelotor at this time. Please see the concerns we outlined below:

Definition of Value

Historically, efforts to fight SCD have been slow and underfunded. Disparities in research innovation for SCD, when compared to other diseases are well documented, and have consequently led to lack of treatment options and high mortality rates for people with SCD. Recent scientific discoveries have led to the development of new treatments, many of which are currently in the pipeline and have provided the community with hope for improved quality of life in the future. Given the lack of current Food and Drug Administration (FDA) approved medications for SCD, special considerations are necessary to provide greater transparency and to incorporate more nonmedical and indirect costs in the review, and to better contextualize value assessments. We urge ICER to work collaboratively with SCD stakeholders and develop a comprehensive definition of value that can be used to assess this population.

Limitation of Comparators

SCD is defined by a group of genetically and clinically heterogenous diseases that share biochemical and physiological similarities. This leads to a range of acute and chronic complications, driven by ongoing vaso-occlusion. Currently, we lack a clear understanding of the underlying mechanisms that result in the diverse manifestations (e.g. acute chest syndrome, pulmonary hypertension, renal dysfunction, strokes). Comorbidities differ for each individual with and each genotype of the disease, which lead to unpredictable disease progression.

Although evidence-based guidelines exist, they are not widely used or implemented as standard of care. Therefore, treatments should not be classified as "usual care." Treatments for SCD range from opioid administration, body system evaluations to surgical interventions, and other medical treatments. Moreover, hydroxyurea, blood transfusions, and oral L-glutamine (Endari™) therapy are inappropriate for comparison in this review. These disease-modifying treatments utilize different mechanisms of action and, therefore impact diverse clinical outcomes. Other real-world challenges including treatment access, insurance coverage, and patient adherence need to be

considered in ICER's comparative cost effectiveness analysis. Unfortunately, the aforementioned treatments may be limited based on age, location, genotype of SCD, disease severity, and socioeconomic status.

ICER's assessments rely heavily on evidence from randomized clinical trials (RCTs). We are concerned about the potential lack of an adequate representation of the SCD patient population in these trials. The clinical trials under review may represent a minority of the targeted patient population. Additionally, certain populations such as uninsured, socioeconomically disadvantaged, and rural populations are often under-represented in clinical research. To improve the accuracy of the value assessment, ICER should consider incorporating real-world evidence (RWE), such as cost of multiple treatments to treat comorbidities in SCD patients or diversity in different disease severity, in addition to clinical trial evidence. RWE can be better suited to inform payer decision making. ICER should allow sufficient time to elapse after these SCD products are approved and marketed so that RWE can be developed and incorporated into the assessment.

We urge ICER to delay the analyses of sickle cell disease until appropriate comparators are identified and validated with SCD experts.

Health State Categories

As discussed above, symptoms and complications of SCD are different for each person and can range from mild to severe. The scoping document described the use of two health states: SCD with and SCD without VOC. We recommend ICER to consider the review of SCD in different disease state categories: (1) acute events and (2) chronic conditions. The use of these health state categories may allow for a more accurate measurement of cost and outcome associated with states and transitions.

Additionally, health states must be inclusive of other comorbidities of SCD which require medical intervention and cause significant patient burden. These include but are not limited to stroke, acute chest syndrome, splenic sequestration, asthma, end-organ damage, and avascular necrosis (AVN). While VOCs drastically affect the quality of life for people with SCD, VOCs are not the major cause of morbidity and mortality.

Lack of Patient Perspective in the Value-based Price Metric

Individuals with SCD experience complications in multiple organ systems that begin early in childhood and accumulate across the life course. The debilitating nature of SCD impacts social relationships, employment, and the educational attainment goals of patients. SCD disproportionately affects Blacks, African Americans, and Latinx Americans. On top of disease burden, systemic racism, prejudice, and stigma have crippled the SCD community's access to quality care. Likewise, there are notable financial and emotional burdens on the caregivers and families of patients with SCD affecting various aspects of their quality of life including their social and professional achievements.

These "contextual considerations" are not incorporated quantitatively into ICER's suggested value-based price metric. Thus, ICER's value framework fails to capture the significant burden

SCD places on this community. We recommend the quality-adjusted life years (QALYs) analyses account for these "contextual considerations", including non-health benefits, in-direct costs, and societal benefits, such as a faster return to work, improved ability to act as caregiver, better school performance, burden on and costs of caregiving, 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. These indirect costs and non-health factors are of considerable importance to SCD and other rare diseases. We believe the absence of these factors on ICER's value-based price metric significantly limits the review's real-world applicability.

If data describing these factors are unavailable, we recommend that ICER capture and quantify the patient perspective through qualitative assessments. We recommend that ICER solicit in-depth patient, caregiver, and provider interviews on the topics of 1) disease burden and unmet need, 2) current treatment benefits and harms, and 3) reduction of important health disparities. We urge ICER to prioritize the evaluation of the qualitative data and ensure that value is formally and robustly assessed from the patient perspective.

We welcome further discussion about the concerns and recommendations outlined above. We hope that ICER will take into consideration the request from the community and postpone the review of sickle cell disease until more research and insights are available to inform an appropriate methodology. We hope to see increased transparency in disease state selection in future reviews, and that ICER's approach includes contextual considerations, patient engagement, and use of qualitative data.

Sincerely,

Axis Advocacy

Cayenne Wellness Center

Cystic Fibrosis Research, Inc.

Kids Conquering Sickle Cell Disease Foundation

Maryland Sickle Cell Disease Association

The Martin Center Sickle Cell Initiative

SCD Forum

Sick Cells

Sickle Cell 101

Sickle Cell Disease Association of America

Sickle Cell Disease Association of America, Michigan Chapter, Inc

Sickle Cell Disease Association of America, Philadelphia/Delaware Valley Chapter

Sickle Cell Disease Association of America, St. Petersburg Chapter

Sickle Cell Disease Association of Illinois

The Sickle Cell Experience

Sickle Cell Thalassemia Patient Network

Sickled Not Broken Foundation, NV

Supporters of Families with Sickle Cell Disease, Inc.

Tova Community Healthy, Inc.

Uriel Owen Sickle Cell Disease Association of the Midwest

International Association of Sickle Cell Nurses and Professional Associates

Individual Community Stakeholders

Lewis Hsu, MD, PhD, Pediatric Hematologist in Chicago

Kim Smith-Whitley, MD, Pediatric Hematologist in Philadelphia

Yvonne M. Carroll, RN, JD, Sickle Cell Advocate