



February 20, 2020

2020

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Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review (ICER)
Two Liberty Square
Boston, MA 02109

Re: ICER's Assessment of Treatments for Sickle Cell Disease

Dr. Pearson,

The American Society of Hematology (ASH) appreciates the opportunity to offer comments in response to the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report: Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value.

ASH represents more than 18,000 clinicians and scientists worldwide who are committed to the study and treatment of blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sickle cell anemia, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy.

ASH has been engaged throughout ICER's sickle cell disease (SCD) assessment and is still concerned that this review is premature and does not take into account extenuating circumstances. The Society understands that it typical for ICER to review not-yet-approved or just recently approved drugs. ASH, however, has tried to stress why the SCD community is unique and outline our concerns about the potential adverse impact ICER's assessment could have on recent and future progress of new therapies – **the SCD community is on the cusp of benefiting from new, potentially life-changing, treatments and cannot afford a setback.** This remains a concern for the Society and is outlined in the comments below.

2020-2023 Value Assessment Framework

The Society is aware of ICER's new 2020-2023 Value Assessment Framework, just finalized January 31, 2020. While the document is meant to guide future ICER assessments, ASH believes that reviews, such as the current SCD assessment, should also benefit from many of the changes outlined in this new framework, including the two noted below.

- **Augmenting Efforts to Use Real-World Evidence:** For drugs that were approved under accelerated approval pathways, ICER will pilot a formal process to update the original assessment after the treatment has been on the market for at least 24 months to explore how best to develop and assess new real-world evidence.

- **Creating a New Process for Re-evaluating Evidence:** One year after the release of each Final Evidence Report, ICER will formally reassess whether new evidence has emerged that should be included in an update to the report.

The studies used for ICER’s assessment – the SUSTAIN trial for crizanlizumab and the HOPE trial for voxelotor – represent only one trial on acute use for each of these treatments. While this is the evidence that is currently available, it may not be representative of what the research and medical community may learn about these drugs in the future. ASH members believe these treatments will have positive long-term impacts on the quality of life for individuals living with SCD that likely will also impact end organ disease outcomes and survival for patients. Because these drugs were just recently approved, these impacts have not yet been realized. Real world patient experience is difficult to demonstrate in a clinical trial and to account for in models. This is especially true in models where the drug has never been used in long term settings, for any disease, from which to extrapolate or estimate.

Patient Perspectives

ASH would like to thank ICER for the time and dedication the Institute put into understanding the perspectives of SCD patients. The Society appreciates that the report captures that “the way patients with SCD have been treated in the US is a tragedy that has extended over many decades,” that “patients and their families have experienced neglect, racism, and total disregard,” and that the “overall ‘system’ of health insurance and care has betrayed the SCD community.” These powerful statements touch on the unfortunate reality of what hematologists see every day when treating individuals with SCD. While comprehensive, the patient perspectives section could go even further by capturing that some individuals with SCD experience post-traumatic stress disorder related to severe episodes of illness. Furthermore, many adult SCD patients often need to bring an advocate for emergency care to increase the chance of receiving appropriate treatment for pain. The SCD patient population faces varied and severe challenges that are extremely difficult to capture in a report. We believe these issues should be strongly considered as factors that “reduce important health disparities” in a vulnerable population experiencing “particularly high severity in terms of impact on length of life and/or quality of life” and a “high lifetime burden of illness”, as listed in Table 6.1. Potential Other Benefits or Contextual Considerations.

Interpretation of Clinical Data

ICER’s report states that although crizanlizumab reduced pain crises, it is unclear if the reduction seen is enough to produce a meaningful improvement in quality of life for patients. While one pain event might seem insignificant in terms of an assessment of clinical or cost effectiveness, it is likely very significant to the individual experiencing these severe pain crises and extends beyond the two weeks of decreased utility included in the model to include school, work and family disruption. As stated above, no report or model can fully capture the extreme challenges of living with SCD nor the impacts that a particular treatment might have on an individual patient, let alone the community of patients with SCD who suffer from severe pain. ASH looks forward to seeing the results of the patient and caregiver survey and hopes to have an opportunity to review the resulting changes to the draft report in advance of the public meeting. For example, the crizanlizumab study showed that 35.82% of participants in the treatment arm vs. 16.92% in the placebo arm ($p=0.013$) experienced zero pain crises (Table 4.2). The potential to eliminate pain crises would have profound effects on the lived experience of patients with SCD in ways that are not captured in your analysis but hopefully will be revealed in your survey.

Potential Other Benefits

ICER’s report includes an opportunity to provide information on potential other benefits offered by the interventions to the patient, caregiver, delivery system, other patients, or the public that may not have been considered as part of the evidence on comparative clinical effectiveness or cost-effectiveness. For this section, ASH would again like to highlight the potential positive long-term impacts these treatments could have on the quality of life and on end organ disease for individuals living with SCD. It would be impossible to fully consider

these benefits as part of the evidence on comparative clinical effectiveness because these drugs were too recently approved, and these potential long-term impacts are not yet realized. As noted in your report, all treatments evaluated are projected to increase life expectancy, which is an especially important goal in a population whose life expectancy is 20-30 years less than the U.S. general population.

An additional potential other benefit for consideration is the increased interaction with health care providers as a result of crizanlizumab being an infused treatment every four weeks. This increased interaction may permit additional services to be delivered at these scheduled visits, further improving patient outcomes. ASH believes that all of these new treatments have the potential to improve connections between this vulnerable patient population and health care providers.

Thank you for the opportunity to submit comments. Should you have any questions or if you would like to discuss these comments further, please reach out to Leslie Brady, ASH Policy and Practice Manager, at lbrady@hematology.org or 202-292-0264.

Sincerely,

A handwritten signature in black ink, appearing to be 'S. Lee', written in a cursive style.

Stephanie J. Lee, MD, MPH
President



February 20, 2020

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,

On behalf of the approximately 1,000 persons diagnosed with Sickle Cell Disease (SCD) who we serve in California, I am writing to express our concerns about the potential negative impact that your "Sickle Cell Disease: Draft Evidence Report" could have on our community.

Sickle Cell Disease is a multi-faceted condition that exerts extreme hardships on patients and their families. At Cayenne Wellness Center, we are witnesses to these hardships daily. Personally, I attend 10-12 funerals a year celebrating the life the patient lived well before their time. And for each one of them I know that had these drugs been available, affordable and accessible, many of them would still be around to be a mother to their children or a partner to their spouse.

First is the fact that due to the extreme, unbearable pain, many patients are unable to work and/or attend school. Working gives people a sense of identity, belonging and quality of life. Education allows people to better themselves and their families' lot in life. If there is a treatment that can assist patients with staying out of the hospital to be able to work and/or go to school, it is paramount to give them access to such treatment.

Second, as a result of the pain, patients inevitably endure depression, hopelessness and loss of the desire to live. Some have even said, "I would be better off having cancer or HIV/AIDS because at least I wouldn't be discriminated against." This thought should never come to mind in any patient. If there is a treatment that can reduce the occurrence of pain episodes and hospitalizations, it will inevitably allow patients to have a sense of hope and purpose, then I say give them access to this life-changing treatment.

Third, the constant damage that the sickling wreaks havoc on various organs, resulting in a diminished quality of life. If there is a treatment that can slow the effects of sickling so that patients quality of life is extended, then again I say, it is paramount give them access.

The drugs illustrated in your report, crizanlizumab and voxelotor, have the potential to improve the quality of life and extend life for SCD patients. What concerns me is why would anyone want to interfere with any person having quality of life? Why would anyone want to interfere with a person's ability to turn depression and hopelessness, into joy and thankfulness? Why would anyone want to interfere with a person's ability to work/go to school and contribute to society? Why would anyone want to interfere with a person's ability to finally have dignity and not be constantly beaten down?

Dr. Pearson, you can make history. For the first time in our community, YOU can be that person that considers the unmeasured costs of Sickle Cell Disease before releasing your evidence report in March. YOU can strongly emphasize the significant immeasurable value of patient quality of life and improvements in life expectancy. YOU can tell our community that Sickle Cell Lives Matter. That they matter. Dr. Pearson, YOU can tell me that I matter as I am also an individual living with Sickle Cell Disease.

Respectfully submitted,

Carolyn Rowley, PhD
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February 20, 2020

Steven D. Pearson, MD, MSc, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

RE: Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value Draft Evidence Report

Dear Dr. Pearson,

Based on an Emmaus internal clinical review of the ICER Sickle Cell Disease Draft Evidence Report, there have been issues identified that Emmaus believes misrepresent clinical data and the cost-effectiveness of L-glutamine therapy in sickle cell disease. These measures should be corrected in order to produce an objective cost-effectiveness analysis.

Issues to be discussed below in detail:

1. Rate Ratio (Effect Size) Selection
2. Safety Profile of L-Glutamine
3. Uncertainty of Data
4. Concern for Publication Bias

1. Rate Ratio (Effect Size) Selection

1.1 ICER selects the least favorable rate ratio from FDA's exploratory sensitivity analyses as "Treatment Effect" for ICER economic calculations.

(ICER Draft Report, page 53) *"As reported in Table 4.11 the investigator's imputation method resulted in a median count of 3 crises in those treated with L-glutamine versus 4 in those treated with placebo. However sensitivity analyses conducted by the FDA systematically adjusting for non-completers, study group, stratification factors, time on study, baseline age, and baseline crisis counts resulted in a median count of 3.9 crises in those treated with L-glutamine and 4.3 in those treated with placebo, with a rate ratio of 0.91 (0.73-1.12)."*

This **0.91** rate ratio (calculated by dividing 3.9 by 4.3) selected by ICER from FDA's exploratory analysis is inappropriate and detrimentally underestimates the effect size (**Figure 1**).¹ This is clear under "Model Inputs", "Treatment Effect", ICER report page 68 Table 5.12, where 0.91 is noted to be sourced from FDA's multiple imputations whereas other drug treatment effects in the table are calculated from published values (**Table 1**). This exploratory FDA ratio (0.91) is carried throughout ICER's economic calculations (**Table 2** and **Table 3**).

The FDA never concluded that L-glutamine's effect size should be based on the worst-case outcome from an exploratory analysis (0.91). Based on the 'Conclusions and Recommendations' section of the FDA Clinical Review, the effect size of L-glutamine is equal to the Hazard Ratio of

0.73 using a recurrent event analysis.¹ This recurrent event analysis was FDA’s answer to missing data, not the exploratory analyses that ICER presented, which used negative binomial regression (NBR) (**Figure 2** and **Table 4**).

In the ‘Conclusions and Recommendations’ section of the Clinical Review, FDA only specifically mentions the findings of the recurrent event analysis:

(FDA: Endari Clinical Review, page 58) *“FDA analyses considered alternative methods of handling incomplete crisis event counts that did not rely on imputation of incomplete counts and incorporated relevant study information such as the time spent on treatment before dropping out of the study. Particularly, a recurrent time-to-event analysis performed by FDA estimated sickle cell crisis rates per 48 weeks of 3 crises for patients treated with Endari vs. 3.8 crises for patients treated with placebo (HR: 0.73, 95% CI: [0.55, 0.99]).”* (emphasis added).

Referring to **Figure 1**, three exploratory sensitivity analyses were carried out by the FDA. The Fully Conditional Specification (FCS) method is the most conservative method, yielding the worst possible rate ratio using NBR. The FCS approach involved multiple imputations adjusting for numerous variables that were and were not pre-specified: a) treatment group (Endari vs placebo), b) study site (5 regions), c) baseline hydroxyurea use, d) age, e) baseline crisis counts, and f) time spent on study to impute crisis counts for 24 patients that left the study early with crisis counts of “0” (**Figure 1**). The rate ratio (0.91) is not only used to account for acute crises in the ICER model (See ICER Draft Report Table 5.12), but also carries over into the calculation of other acute complications (**Table 2**); for example, in the derivation of “42.25” for acute pain crises, thereby diminishing L-glutamine effect over the lifetime by using this incorrect rate ratio.

This must be corrected in ICER’s Report. For crizanlizumab, ICER used the ratio of the annualized median as published NEJM article (1.63 divided by 2.98 = **0.547**).²

For a more direct comparison, L-glutamine phase 3 study yielded annualized medians of 2.4 for L-glutamine and 4.3 for placebo which would yield a rate ratio of **0.558** (p=0.02; CMH with modified ridit).³

Action required: For consistency, ICER must use information contained within both the FDA package insert and Emmaus’ *NEJM*-published (non-annualized) median difference of 3 divided by 4 = **0.75**; or the Endari package insert recurrent-event time analysis intensity rate ratio = **0.75**; or the recurrent event-time analysis as performed by the FDA reviewers hazard ratio = **0.73**.^{1,4,5}

1.2 ICER omits key information (“exploratory analyses”) from an FDA quote

ICER presents partial quotes from the FDA Clinical Review that may incorrectly portray FDA’s conclusion. ICER Draft Report, page 46, ICER writes: *“The FDA conducted several sensitivity analyses using different assumptions about the dropout data. Their analyses suggested that the reduction in crises from L-glutamine versus placebo ranged from 0.4 to 0.9. Consequently, FDA concluded that the results show a ‘modest trend supporting a claim of benefit for [L-glutamine]’, but noted that in some analyses, the upper limits of the confidence intervals for rate ratios comparing the treatment groups included 1.”* (emphasis added).

What the FDA actually said:

(FDA: Endari Clinical Review, page 13) *“In sensitivity analyses conducted by FDA, the reduction in crises over 48 weeks from L-glutamine treatment compared to placebo ranged from 0.4 to 0.9 crises. Together, these exploratory analyses can be interpreted as showing a modest trend supporting a claim of benefit for Endari.”* (emphasis added).

ICER’s statement implies FDA concluded that the results overall show a modest trend for benefit. In contrast, what FDA said was, *“Together, these exploratory analyses can be interpreted as showing a modest trend supporting a claim of benefit for Endari.”*(emphasis added).¹ The exploratory analyses that FDA conducted not only takes into account multiple additional imputation factors, but also were analyzed using negative binomial regression. This is a different statistical method than Cochran-Mantel-Haenszel, the test statistic used to analyze the primary endpoint.

Action required: ICER needs to make it clear that the FDA is referring to exploratory analyses in the above statement.

2. Safety Profile of L-Glutamine:

2.1 Emmaus disagrees with ICER regarding the safety of L-glutamine. ICER concludes:

(ICER Draft Report, page 57) *“However, with residual safety concerns and uncertainty about the clinical benefits due to trial limitations, we feel there remains a small risk that L-glutamine produces net harm overall, but that this risk is less than 10%.”* (emphasis added).

ICER misinterpreted the dosing information from the REDOXs study and subsequently misconstrued concerns over increased mortality with L-glutamine use:

(ICER Draft Report, page 49) *“However, the safety data on L-glutamine from trials in other conditions provides less reassurance. The REDOXs trial of critically ill patients with multiorgan failure reported that patients treated with 0.35 g/kg/day of IV glutamine had significantly higher in-hospital mortality and mortality at 6 months than patients who did not receive L-glutamine.”* (emphasis added).

The dose given in the REDOXs study was much higher than the recommended maximum dose of L-glutamine in sickle cell disease.⁶ The study also used different formulations of glutamine and also included the intravenous route of administration in critically ill patients with multiorgan failure, not sickle cell patients.⁶ Dipeptides (not L-glutamine) were administered as follows: 0.5 g/kg/day of **IV alanyl-glutamine** and 42.5g per day of both **oral alanyl-glutamine and glycine-glutamine**.⁶ This results in approximately 0.35 g/kg/day IV glutamine and 30 g/day of oral glutamine. For varying body weights, a table has been created to show that administration of these mixtures of dipeptides would have led to between 182% to 370% of total daily recommended dose of L-glutamine in SCD as shown in **Table 5**.

Because of these factors, alongside the fact that these patients were not sickle cell patients but critically ill, multi-organ failure patients, FDA stated that,

(FDA: Endari Clinical Review, page 103) “Two other studies of interest (Heyland, Muscedere et al. 2013, van Zanten, Sztark et al. 2014) [...] reported an increase in mortality among critically ill patients who received parenteral nutrition containing glutamine. These studies were conducted in critically ill, mechanically ventilated patients with severe sepsis and multi-organ failures, and included both intravenous and enteral supplementation. The findings from these studies are therefore not applicable to the patient population for whom Endari use is being sought in this application.” (emphasis added).

Action required: ICER has incorrectly referenced a study, consequently misconstruing the safety profile of L-glutamine in sickle cell disease at the prescribed dose level. Based on these reasons, ICER’s conclusion that there is a risk that L-glutamine produces net harm overall should be withdrawn.

3. Uncertainty of Data:

3.1 In ICER’s assessment of the L-glutamine Phase 2 clinical trial:

(ICER Draft Report, page 30) “We considered the Phase II trial of L-glutamine to be poor quality because of differences in the groups assembled at baseline, a large and differential rate of drop-out, and inadequate control for potential confounders (e.g., hydroxyurea use).” (emphasis added).

The Phase 2 clinical trial was a proof of concept study and study data were integrated with the phase 3 data only for FDA safety analyses, not for efficacy.

3.2 ICER’s assessment of the L-glutamine Phase 3 clinical trial:

(ICER Draft Report, page 30) “We rated the Phase III trial of L-glutamine to be fair quality because there was a high and different loss to follow-up between groups; statistical imputation to account for these differences may have introduced further bias.”

ICER refers to discontinuations and imputations:

(ICER Draft Report, page 46) “Due to the high and differential rate of trial discontinuation prior to the completion of the 48-week treatment period, investigators in the Phase III study imputed the crisis results [...] This method may have introduced bias in the results because the high number of non-completers meant that the large proportion of imputed counts may have changed the distribution of data.”

At first glance, there may appear to be bias in favor of glutamine by using the protocol pre-specified imputation method (ICER Draft Report page 46) where patients were imputed with a value of 3 crises for the glutamine arm and 4 crises for the placebo arm. Because of the differential dropout rate (glutamine > placebo by 12%) more imputations were made in the L-glutamine arm where patients exited the study with 0, 1, and 2 crises than those in the placebo arm. More crises were added to the glutamine arm (106) than the placebo arm (34).³ Keeping in mind the 2:1 randomization, this evaluation showed that the imputation method as pre-specified in the protocol did not bias the results in favor of L-glutamine (Table 6).

Table 6 – Number of SCCs at Time of Withdrawal that Resulted in Imputations

Number of SCCs at Time of Withdrawal	L-Glutamine (N = 55)	Placebo (N = 19)
0	20	4
1	20	2
2	6	4
3	N/A*	4
Total Number of Crises Imputed	106	34

Source: Data on File

*Not included for this analysis because an SCC total of 3 or higher in the L-glutamine group would use the patient's actual count rather than imputed count

An additional analysis was performed taking into consideration time on study using the pre-specified imputation method and found that 3.37 and 3.40 events per patient-year were added to non-completers in the L-glutamine and placebo groups, respectively.³ This evaluation supports the fact that the imputation method pre-specified in the protocol did not bias the results in favor of L-glutamine.

ICER criticizes the L-glutamine study for high discontinuations

While ICER criticizes the “large rate of trial discontinuation” in the L-glutamine study (throughout their document), ICER omitted mention of dropout rates in other sickle cell trials, in particular, the SUSTAIN trial. The Phase III study of L-glutamine overall dropout rate was 32% while the discontinuation rate in the SUSTAIN trial was 35%.^{2,4}

ICER also refers to imputations for missing values only for the L-glutamine study

ICER omitted mention of imputations being made when calculating “annualized medians” as performed in the crizanlizumab study. From the crizanlizumab *NEJM* publication itself: *“The crisis rate for every patient was annualized to 12 months. The annual crisis rate was imputed for patients who did not complete the trial.”* (emphasis added).²

Using an annualized imputation method, one cannot impute for zero counts at early discontinuation

Referring to the SUSTAIN trial, ICER states “At the end of the treatment phase, 36% of the crizanlizumab group had a crisis rate of zero, compared to 18% of the placebo group.” (ICER Draft Report, page 33). In comparison, the L-glutamine phase 3 study had 23% (35/152 patients) in the treatment arm with a crisis rate of zero as compared to 10% (8/78 patients) in the placebo arm.³

Action required: ICER should remain consistent across studies in sickle cell disease when referring to high discontinuation rates and raising the issue of uncertainty in study endpoints due to imputations. We request ICER to refrain from overly criticizing the dropout rate and subsequent imputations in the phase 3 trial of L-glutamine.

4. Concern for Publication Bias:

4.1 After reading the FDA clinical review of L-glutamine, ICER expressed concerns for publication bias regarding L-glutamine:

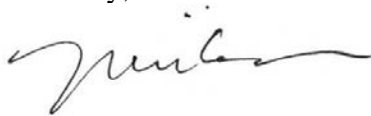
(ICER Draft Report, page 45) *“Two additional Phase II studies were identified in our review of the FDA clinical review packet for L-glutamine and the clinicaltrials.gov site that would have matched our PICOTS criteria for inclusion. Both trials seemed to have been completed more than two years ago, yet our literature search did not find any publications related to these trial. We have summarized the limited information we have for these two studies in Appendix Table D18, but note that there may be potential publication bias in the evidence supporting L-glutamine.”* Emmaus understands ICER’s concern related to the lack of public disclosure of data related to the two studies listed in **Table 7**.

Study 8775, noted in ICER Table D18, was an early proof-of-concept conducted to evaluate the frequency of sickle cell crises, number of hospitalization days, number of painless days on study, and safety. This study enrolled patients between December 1998 and January 2003. Since only 6 out of 24 patients completed the trial, there was insufficient data for primary endpoint analysis. Nevertheless, the study was presented as an abstract by Koh et al., at the Sickle Cell Disease Association of America meeting in Covington, Kentucky and the 28th National Sickle Cell Disease Program in April 2005. **Note: There is an apparent typographical error in the “Results” column of the ICER Table D18** where “there was a significant increase in the number of **pain** days...” should read “there was a significant increase in the number of **painless** days”. From the FDA Clinical Review, page 35, *“In the 6 evaluable subjects, there was a significant increase in the number of painless days ($p = 0.00885$).”* This is pointed out to ICER in order to alleviate any concerns by readers that this study was unpublished because of a negative finding (such as increased pain-days).

Study 10511, noted in ICER Table D18, was an early proof-of-concept that studied the effect of L-glutamine on exercise tolerance in sickle cell patients. This study enrolled 15 subjects between February 2004 and August 2008. The key efficacy parameters describing exercise endurance were peak work rate (watts) and endurance (minutes). The exercise test was performed at baseline and at Week 10. This study was not published because it did not reach the targeted enrollment of 50 subjects and the decision was made to terminate the study.

Actions required: 1) ICER to correct language in their table D18 to change “pain days” to “painless days”. 2) ICER to remove *“but note that there may be potential publication bias in the evidence supporting L-glutamine.”* from their draft report.

Sincerely,



Yutaka Niihara MD, MPH
Chairman and CEO, Emmaus Life Sciences, Inc.

References

1. Food and Drug Administration. Center for Drug Evaluation and Research. Application Number 208587Orig1s000. Clinical Review of L-Glutamine (Endari). 2019; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208587Orig1s000MedR.pdf
2. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. *New Eng J Med.* 2017;376(5):429-439.
3. Data on File.
4. Niihara Y, Miller ST, Kanter J, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. *New Eng J Med.* 2018;379(3):226-235.
5. Administration FaD. Endari (l-glutamine oral powder) [package insert] Emmaus Medical Inc. 2017.
6. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. *New Eng J Med.* 2013;368(16):1489-1497.

APPENDIX TO PUBLIC COMMENT STATEMENT

Figure 1 – FDA Exploratory Analyses Comparing Rates of Sickle Cell Crisis Events Per 48 Weeks Using Negative Binomial Regression – [\[Back to Text\]](#)

FDA strategy for handling incomplete crisis counts	Rate of crises/48 weeks L-glutamine vs Placebo	Rate Ratio [95% CI] Based on Negative Binomial model
FDA sensitivity analysis population N=206	3.3 v 4.1	0.80 [0.64, 1.01]
ITT population, assuming incomplete crisis counts for 24 patients are "0", N=230	3.3 v 4.2	0.77 [0.61, 0.99]
Multiple Imputation (FCS)* for 24 patients with incomplete crisis counts, N=230	3.9 v 4.3	0.91 [0.73, 1.12]

SOURCE: FDA Reviewer analysis
 All analyses adjusted for region and baseline hydroxyurea use; using time on study as offset
 *FCS = fully conditional specification;
 The multiple imputation approach adjusts for treatment group study site, baseline hydroxyurea use, age, baseline crisis count, and time spent on study to impute crisis counts for 24 patients.

Table 1 – Treatment Effects – [\[Back to Text\]](#)

Treatments	Relative Effect on Acute Pain Crises	Change in Hemoglobin (g/dL)	Source
Crizanlizumab	0.547	0	SUSTAIN trial ¹⁷
Voxelotor	0.868	1.2	HOPE trial ⁵⁹
L-glutamine	0.910	0	FDA Multiple Imputation Analysis⁶¹

g/dL: grams per deciliter

Source: ICER Draft Report – Table 5.12

Table 2 – Comparison of Acute Events – [\[Back to Text\]](#)

Treatment	Optimal Usual Care	Crizanlizumab	Voxelotor	L-glutamine
Acute Pain Crisis	45.56	28.75	43.86	42.25
ACS	0.99	0.75	0.93	0.99
MI	0.151	0.124	0.147	0.151
RI	0.022	0.020	0.021	0.022
Stroke	0.61	0.51	0.38	0.61

ACS: acute chest syndrome, MI: myocardial infarction, RI: renal infarction

Source: ICER Draft Report – Table 5.24

Table 3 – Results for the Base Case for L-glutamine versus Optimal Usual Care Alone

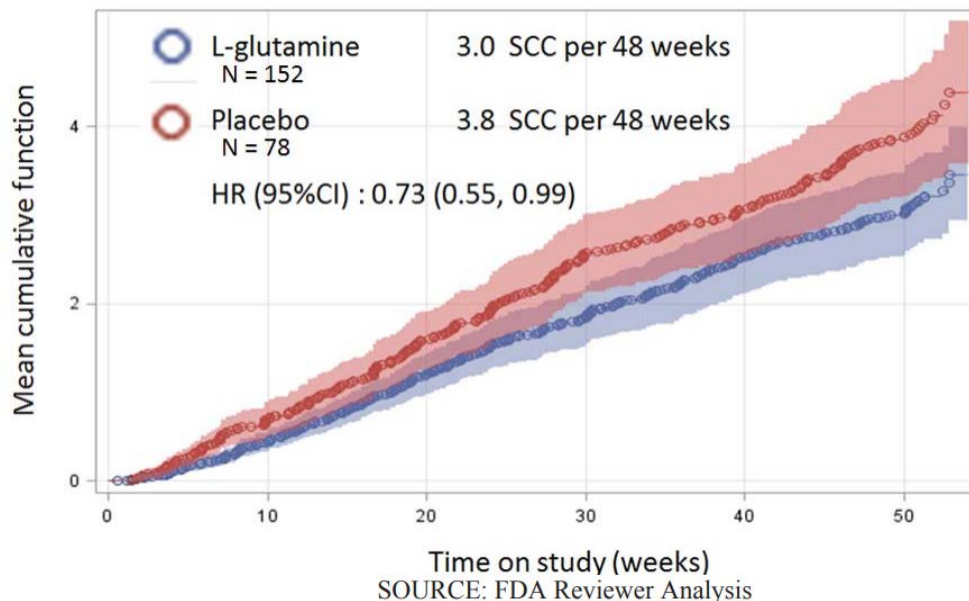
– [\[Back to Text\]](#)

Treatment	Usual Care	L-glutamine	Difference	ICER	
Treatment Cost	-	\$302,000	\$302,000	-	
Other Cost	\$1,145,000	\$1,121,000	-\$23,000	-	
Total Cost	\$1,145,000	\$1,423,000	\$278,000	-	
Acute Pain Crises	45.56	42.25	-3.31	\$84,000	per acute pain crisis avoided
Hemoglobin (g/dL)	0.00	0.00	0.00	Dominated	
LYs	15.19	15.48	0.29	\$965,000	per LY gained
evLYG	7.64	7.97	0.33	\$847,000	per evLYG gained
QALYs	7.64	7.75	0.10	\$2,717,000	per QALY gained

evLY: equal value life year, evLYG: equal value life years gained, g/dL: grams per deciliter, ICER: incremental cost- effectiveness ratio, LY: life year, QALY: quality-adjusted life year

Source: ICER Draft Report – Table 5.23

Figure 2- FDA Analysis: Mean cumulative functions for sickle cell crisis events by treatment group – [\[Back to Text\]](#)



(FDA: Endari Clinical Review, page 50) *“An alternative analysis was performed by FDA in an effort to overcome the difficulties caused by the incomplete data records. A recurrent event analysis based on the proportional rate regression model (Lawless and Nadeau, 1995; Lin et al., 2000) was performed by FDA to incorporate information on patients’ time spent on study and to take into account the fact that times between crisis events for a patient are not necessarily independent.”*(emphasis added).

Table 4 – FDA Analysis: Estimated 48-week sickle cell crisis event count by treatment group, recurrent event analysis, ITT population (N = 230) – [\[Back to Text\]](#)

	L-Glutamine (N = 152)	Placebo (N = 78)
Estimated SCC event count (95% CI)	3.0 (2.5, 3.4)	3.8 (3.1, 4.5)
Hazard Ratio, L-Glutamine vs Placebo (95% CI)	0.73 (0.55, 0.99)	

Source: FDA Reviewer Analysis

Table 5 – Weight Based Doses of Glutamine in the REDOXS trial compared to Endari [\[Back to Text\]](#)

Pt Wt. (kg)	IV dose (g) (0.35 g/kg)	IV dose + 30g PO dose (g)	% of Endari Dose
20	7	37	370%
30	10.5	40.5	203%
40	14	44	220%
50	17.5	47.5	238%
60	21	51	255%
70	24.5	54.5	182%
80	28	58	193%
90	31.5	61.5	205%
100	35	65	217%

Table 7 — Unpublished L-glutamine Studies – [\[Back to Text\]](#)

Unpublished L-Glutamine Studies (Food and Drug Administration, Center for Drug Evaluation and Research, 2019, 23)						
Title / Trial Sponsor	Study Design	Study Arms	Patient Population	Primary Outcomes	Results	Completion Dates
L-Glutamine						
L-Glutamine Therapy for Sickle Cell Anemia NCT00586209 Sponsor: Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center Collaborator: Emmaus Medical Inc.	Prospective Phase II, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Assignment Enrollment: 15 4-week screening period 12-week treatment period 5 week tapering period	<u>Intervention:</u> Weight-based L-Glutamine with upper limit of daily dose at 30g/day (n=5) <u>Comparator:</u> Placebo (n=10)	<u>Inclusion:</u> 1. Subjects (≥18 years of age) with sickle cell anemia or sickle β ⁰ -thalassemia. 2. At least two episodes of painful crises within 12 months of screening <u>Exclusion:</u> 1. Significant medical condition requiring hospitalization within 2 months of screening 2. Diabetes mellitus with untreated	1. Number of occurrences of painful sickle cell crises	Adverse Events n (%) L-Glutamine: 4 (80) Placebo: 7 (70) Serious Adverse Events n (%) L-Glutamine: 2 (40) Placebo: 5 (50) Diarrhea L-Glutamine: 2 (40) Placebo: NR Nausea / Vomiting L-Glutamine: 2 (40) Placebo: NR Sickle Cell Crisis	November 2009

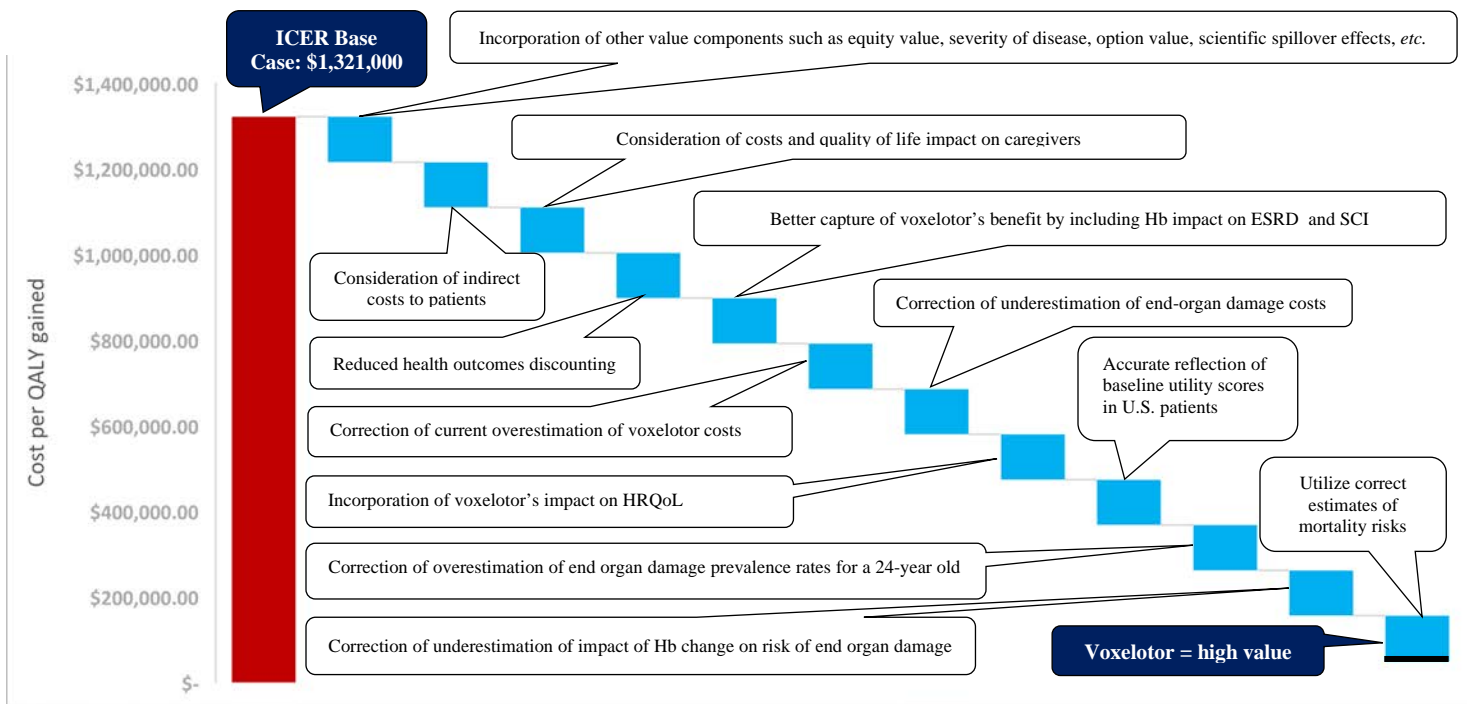
			fasting blood sugar >115 mg/dL		L-Glutamine: 1 (20) Placebo: NR Hypertension L-Glutamine: 1 (20) Placebo: NR	
Legacy Study 8775	Phase 2a, Randomized, Single-Center, Double-Blind, Placebo-Controlled Crossover <u>Enrollment:</u> 24 24-week treatment period followed by 5 week tapering period prior to crossover	<u>Intervention:</u> Oral L-Glutamine 30g/day (10 g, TID) <u>Comparator:</u> Placebo	<u>Inclusion:</u> 1. Subjects (≥18 years of age) with a diagnosis of sickle cell anemia 2. At least 3 episodes of painful crises during the 12 month period prior to randomization <u>Exclusion:</u> None Reported	1. Total NAD 2. NAD redox potential 3. RBC endothelial cell adhesiveness 4. Hematologic parameters 5. Frequency of painful crises 6. Number of hospitalization day 7. Number of painless days 8. Safety.	Of the 6 evaluable patients, there was a significant increase in number of pain days (p=0.00885). The improvement in number of painful crises was not statistically significant (p=0.28).	Unknown
NAD: nicotinamide adenine dinucleotide, NR: not reported, RBC: red blood cell, TID: three times a day					Source: ICER Report, Table D18	

GBT appreciates the opportunity to comment on ICER's Draft Evidence Report for crizanlizumab, voxelotor, and l-glutamine for Sickle Cell Disease (SCD). SCD is a unique disease that affects a historically overlooked, underserved, and underrepresented population. With limited investment, only a few treatment options were available for SCD before 2019, a challenge compounded further by the inadequate access SCD patients have to quality health care services. The annual cost of medical care in the U.S. for people who suffer from sickle cell disease exceeds \$1.1 billion.¹ Moreover, care for SCD patients with complications can cost the healthcare system more than \$250 thousand dollars per patient per year, a cost that can be offset by novel disease modifying treatments, which also improve patient outcomes and quality of life. Oxbryta™ (voxelotor) was approved by the FDA under accelerated approval due to limited treatments options and the urgent need to address the symptoms, morbidity, and mortality in SCD that are not attended to by optimal usual care (OUC). As a result of these challenges, including the nascent stage of investment in SCD treatments relative to other diseases, we believe it is wholly unnecessary for ICER to conduct a value assessment of novel SCD treatments. **Patients are more likely to be harmed than helped by ICER's assessment which inaccurately characterizes the potential value of novel therapies.**

While GBT does not believe ICER's assessment of SCD therapies is appropriate, our substantive concerns about ICER's draft evidence report can be summarized in two points:

- 1) Voxelotor's evidence rating should be higher considering the totality of the evidence around voxelotor's efficacy and the role of Hb as the most important independent predictor for end organ damage (EOD) and survival in SCD; and
- 2) Voxelotor offers good value for patients and the SCD community, if assessed with the appropriate value framework and model parameters (See Figure 1 below).

Figure 1: Conceptual illustration of why voxelotor offers good value for patients and the SCD community if assessed with appropriate value framework and model parameters



Based on the above two points, our detailed comments are outlined below:

1) Voxelotor's evidence rating should be higher considering the totality of the evidence around voxelotor's efficacy and the role of Hb as the most important independent predictor for end organ damage and survival in SCD.

Hb is the most important indicator in predicting risk of end organ damage in SCD and survival.

Specifically, deoxygenated HbS polymerization is central to the cause of SCD (as it drives the molecular pathogenesis). Thus, by inhibiting HbS polymerization in red blood cells, increasing Hb and reducing hemolysis, voxelotor has the potential to modify outcomes in SCD, which should be reflected in ICER's evidence report.² Equally, HbS polymerization is extraordinarily sensitive to deoxygenated HbS concentration, such that even tiny modifications in concentration result in sizable effects on polymerization.^{3,4}

Any clinical or value assessment of voxelotor should reflect the current regulatory understanding of the role of Hb in SCD.

The importance of both Hb and inhibiting HbS polymerization in the treatment of SCD was recognized by the Food and Drug Administration (FDA) in granting accelerated approval of voxelotor. The U.S. Congress and the FDA established the accelerated approval pathway for drugs that treat serious conditions, fill an unmet medical need, and are approved based on evidence which is reasonably likely to translate into patient benefit. This balanced approval construct supports an important public policy interest by ensuring patients' timely access to medicines that are safe and highly likely to produce clinical benefit, while the sponsor conducts additional, confirmatory clinical trials as agreed by the FDA.

- **The impact of Hb increase goes beyond what ICER has included in its draft report.** ICER should reflect the full impact of Hb levels on outcomes by capturing the effects of Hb on neurocognitive dysfunction, silent cerebral infarction (SCI), end stage renal disease (ESRD) and survival.
- **Hb increase translates to reduced healthcare utilization and costs.** The benefits of an increase in Hb go well beyond a reduction in end organ damage. Specifically, these positive outcomes often lead to avoidance of low-value spending; reduction in transfusions, reduced patient oxygen dependency, and reduction in the use of erythropoiesis-stimulating agents to treat anemia.^{5,6,7}

By not considering the full effects of improving healthy hemoglobin levels, ICER is underestimating the benefits of an increase in Hb levels and its impact on the disease.

Voxelotor provides clinically meaningful benefit to patients with SCD with a manageable safety profile.

ICER's clinical rating of voxelotor as 'P/I: Promising but Inconclusive' is inconsistent with the totality of available evidence. Voxelotor, as an HbS polymerization inhibitor, reversibly binds to hemoglobin, stabilizing the oxygenated hemoglobin state.⁸ This improvement in Hb levels is a clinically relevant endpoint in SCD and is supported by the American Society of Hematology, evidenced by the FDA's accelerated approval, and supported by numerous clinical studies.^{9,10}

- **In rating voxelotor as 'P/I', ICER's assessment is inconsistent with the available evidence base.** ICER states "*voxelotor did not significantly reduce the annualized incidence rate of acute pain crises and did not improve quality of life.*"¹¹ The HOPE study collected health related quality of life (HRQoL) information from both patients' and clinicians' perspectives with multiple questionnaires. It is premature to conclude voxelotor does not improve quality of life before all the collected information is fully analyzed. In fact, a 2019 ASCAT conference presentation regarding voxelotor's effect on reducing the occurrence and severity of leg ulcers points to potential quality of life improvements.¹² There are additional studies that further demonstrate

HRQoL benefits of voxelotor treatment.^{13,14,15} Ongoing analysis of the HOPE trial and additional studies are expected to provide further evidence on the HRQoL benefits of voxelotor.

- **ICER implies that use of voxelotor does not reduce transfusions, yet studies disprove this.** The HOPE trial did not include patients who were on chronic red blood cell (RBC) transfusions at baseline. SCD patients are transfused for a variety of different reasons beyond anemia; in HOPE, most transfusions were performed because of acute vaso-occlusive crises. In a series of case studies where severely anemic patients were offered voxelotor, there was an observed 60% reduction in transfusions.¹⁶

2. Voxelotor offers good value for patients and the SCD community, if assessed with the appropriate value framework and model parameters.

ICER's framework is fundamentally flawed and unable to accurately assess SCD treatments as it misses multiple value components beyond patient costs and quality of life. GBT does not agree with the application of ICER's value framework and its cost-effectiveness model in quantifying the economic value of innovative SCD treatments like voxelotor, which was approved under FDA's accelerated approval pathway. The systemic issues in SCD, previously mentioned in our open input letter, were not incorporated into the model. In the recently issued ICER 2020 Value Framework, ICER stated that their methodology cannot quantify disparity and equity value in the current framework.¹⁷ This suggests that ICER's value framework is not appropriate for value assessment in SCD. Furthermore, ICER's cost-effectiveness model is ill-suited for orphan diseases such as SCD and for patients who have been historically ignored and underfunded as it disregards other key value components beyond cost and outcomes such as equity value, disease severity, option value, scientific spillover effects, *etc.*¹⁸

Incorporate the impact of SCD on patients & caregivers in the base case. ICER spends a considerable amount of time reflecting on the SCD burden for both patients and their caregivers, yet this is not reflected in the clinical effectiveness and long-term cost-effectiveness assessments. An appropriate value framework for SCD must take on *broad societal perspectives*, considering the disparity these patients face.^{19,20} Further, health disparity does not revolve solely around the life expectancy (LE) gained by patients; rather, it includes many additional components, such as patient quality of life and that of their caregivers. Hence, the *equity value* provided by novel SCD treatments goes well beyond LE gained and should be considered in the base case of the value assessment.

Notwithstanding these concerns, as it specifically relates to the model, ICER's cost-effectiveness model requires significant revisions in terms of both model structure and parameters, as outlined below:

Do not discount the future years of today's SCD patients. ICER's method of discounting negatively targets outcomes that are important to patients by over-discounting benefits that occur after the first year of treatment. Considering a 12-year-old child beginning treatment for SCD, a 3% annual discount rate more than halves actual outcomes (55%) after two decades of treatment. By age 45 (the median age of death), health benefits are worth only slightly more than a third (38%) of their value. In ICER's own sensitivity analyses, eliminating discounting more than halves the cost per quality adjusted life year (QALY) gained in the base case, suggesting a substantial impact of the discount rate on overall results. Even in the U.K., one of the toughest markets to access treatment, there is the application of a lower discount rate for outcomes in treatments that, "*provide substantial effects in restoring health, sustained on a very long period.*"²¹

Employ structural changes by including the impact of Hb on ESRD and SCI and by considering the impact of baseline Hb on incidence rates of acute and chronic conditions. ICER should add SCI and ESRD to the list of outcomes considered in the model. Additionally, ICER needs to control for baseline (BL) Hb to ensure an accurate reflection of voxelotor's benefit in its model. Not all of the source studies referenced in the model had

a baseline Hb similar to the HOPE study (BL mean Hb 8.6 g/dl).²² Baseline hemoglobin plays a central role in incidence rates of acute and chronic conditions.

Correct the overestimation of voxelotor's costs. Voxelotor's costs must be uniform throughout the report, yet ICER uses several values for the annual cost of voxelotor (\$104,357,²³ \$84,000,²⁴ \$99,197²⁵). More consistency and clarity are needed. Also, since each voxelotor bottle is a 30-day supply, ICER overestimates voxelotor's annual cost: 12 bottles and 5-6 pills are needed rather than 13 bottles annually, which carries over into the following year. Overestimation of voxelotor's costs incorrectly lowers the modelled benefit. In addition, the value-based pricing calculations of the three drugs in the draft evidence report are not consistent with the base case model results, which calls into question the internal validity of the report.

Correct the underestimation of end organ damage costs. ICER uses MarketScan analyses of SCD patients for its model, which includes commercial and Medicare populations and supplements this with CMS Medicare data. This approach excludes Medicaid data, which account for more than 50% of SCD patients, and severely underestimates the cost of EOD. ICER should refer to the Xue *et al.*, ASH 2019 presentation for guidance.²⁶

Appropriately quantify voxelotor's impact on quality of life. ICER's model does not give voxelotor any HRQoL benefit based on the results: this is not clinically accurate and challenges the model's underlying validity. In ICER's model, the optimal usual care (OUC) comparator has 15.19 life years (LYs) and 7.64 QALYs, meaning the average utility is 0.503. For voxelotor, with LYs at 17.30 and QALYs at 8.60, the calculated average utility is 0.497. This 1% difference between voxelotor and OUC *incorrectly* suggests that there is no benefit of using voxelotor based on ICER's model in terms of the quality of life rather than years lived. This is despite the model's specific design to show that an Hb increase reduces risk of fatigue, stroke, CKD and PH, which lead to significant decrements in patients' HRQoL.

Revise the SCD baseline utility score to represent U.S. SCD patients so that they are not deprioritized over patients with other diseases. ICER underestimates the baseline utility of patients entering the model. Specifically, ICER derives their baseline utility of 0.71 from a U.K. study, a misinterpretation of this study, where the EQ-5D actually estimated a utility of 0.89 in SCD patients not experiencing pain crisis in the U.K.^{27,28} In addition, there should be a further adjustment to account for the numerous studies that demonstrate differences in utilities between countries for even the same disease.^{29,30,31} Using a lower baseline utility reference from the U.K. decreases the value of SCD treatments for U.S. SCD patients. Even patients who have returned to the model's baseline disease state can never achieve the total absolute QALY gain of patients with other diseases.

Correct the estimated baseline prevalence rates of end organ damage in the modeled population. The baseline prevalence rates for end organ damage for a 24 year old patient with SCD have been overestimated and are not consistent with clinical practice and literature.^{32,33,34,35,36} This failing does not leave much room for future interventions to improve the condition. In fact, the risk of end organ damage increases as patients age. ICER's use of MarketScan analyses of SCD patients for its model includes only commercial and Medicare populations, excluding Medicaid data (which, as mentioned above, constitutes more than 50% of SCD patients).^{37,38} Further this misrepresents the prevalence rates of acute and chronic conditions for younger patients as only 9% of all SCD patients between 18-30 are Medicare or dual eligible beneficiaries: this undervalues the impact of voxelotor.³⁹ By not including such a patient population, ICER does not account for the reality of care and outcomes in SCD.

ICER's inaccurate estimation of prevalence of end organ damage makes the outcomes of patients on voxelotor two times worse, significantly underestimating the value of voxelotor.

Correct the underestimation of 1 g/dL Hb increase's impact on risk of end organ damage.

- **The impact of Hb on risk and burden of stroke are underestimated in the model, decreasing the estimated value of voxelotor.** Stroke's impact on HRQoL and costs should be considered both acute and chronic. The impact of 1 g/dl on risk of stroke using the COOPERATIVE study should also be adjusted for genotype distribution and type of stroke, hence an odds ratio (OR) of 0.583 per 1 g/dl increase in Hb should be employed instead of ICER's value of 0.602.⁴⁰
- **The impact of Hb on risk of PH is severely underestimated.** ICER uses the Caughey *et al.* study, which reports -1% of the delta in prevalence of elevated pulmonary artery systolic pressure (ePASP) observed between patients with mean Hb >8.8 g/dl vs. <=8.8 g/dl, not necessarily for a 1 g/dL change in Hb. In contrast, many other studies have estimated the OR of having an elevated tricuspid regurgitation velocity (TRV) per 1 g/dl increase in Hb, which gives a weighted average OR of 0.600 per 1 g/dl increase in Hb as opposed to the 0.97 calculated OR employed by ICER.^{41,42,43}

These two above mentioned incorrect OR values combined, inflate the cost per QALY gained of voxelotor vs. optimal usual care by nearly 60%, which further decreases ICER's estimated value for voxelotor.

Correct the estimation of the rate of mortality of patients with SCD in the model. SCD patients have a devastating prognosis compared to the general population, and the model should accurately quantify their life expectancy. An accurate mortality rate is crucial as its overestimation will make a treatment appear less effective. ICER overestimates the mortality rate by:

- 1) Adding end organ damage such as stroke, CKD and PH mortality on to measures *that already* capture this in real-world SCD mortality rates.⁴⁴
- 2) Overestimating the impact of end organ damage on mortality:
 - **CKD:** ICER assumed the CKD impact on mortality to have a relative effect of 9.57 based on a study conducted by Dr. Lanzkron, which misinterprets her analyses. The value ICER uses is the impact of having renal disease on the age of death of patients, not the impact on mortality rate. Literature suggests the relative risk to be 1.42.^{45,46}
 - **PH, HF, and MI:** ICER assumed the PH impact on mortality to have a risk factor of 12.57, with heart failure (HF) and myocardial infarction (MI) assumed to have the same effect. 12.57 is based on reference studies that defined PH based on an echocardiogram.^{47,48,49} However, the gold standard for defining PH is based on heart catheterization, wherein the excess risk of death of PH vs. non-PH patients is 2.46.⁵⁰

Combined, the two factors above contribute to an assumption of an excess risk of death, and by doing so more than double the cost per QALY gained.

Conclusion

ICER's value framework, including the evaluation of clinical benefit and application of traditional cost-effectiveness modelling, ignore the severity of the unmet need in SCD, and the potential of novel disease-modifying therapies. Extraordinary pain and fatigue, reduced life-expectancy, poor treatment options and inequity as compared to other diseases *is the base case for SCD patients*. Value assessments for new treatments in SCD must accurately and comprehensively capture the full benefit delivered to patients and their families, or we risk continued under investment in one of our most ignored diseases.

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ICER Review of Voxelotor – Comments & Questions

Regarding: Bradt P, Spackman E, Synnott P, Chapman R, Rind D M, Pearson S. Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value. Institute for Clinical and Economic Review, January 23, 2020. <https://icer-review.org/material/sickle-cell-disease-draft-evidence-report/>

Disclosure: My interest in sickle cell disease stems solely from several projects I was involved in during my Masters of Public Health studies at George Washington University, and the empathy I gained for those with the disease. I have no financial or other conflicts of interest.

To whom it may concern:

I have a few questions/comments regarding a few important assumptions you have made in your report on Voxelotor in your report. While I value ICER's objectives and much of what is in your reports, I have questioned the approach essentially ignoring the development costs and long-term benefits to society for first-in-class drugs and ignoring the eventual pricing pressure from me-too competition and (ultimately) generics that should lower prices after a period. My questions about ICER's voxelotor analysis below, however, relate solely to assumptions used as evidence of treatment effect.

Item 1: Page 37: “At baseline, patient characteristics were balanced across intervention arms”.

This is highly questionable. As you can see in Table 1 of **Vichinsky E. et al, 2019, A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease**, homozygous hemoglobin S (HbSS) comprised 80% in the placebo arm, and 68% in the 1500 mg voxelotor arm. Numerous published articles describe HbSS as having the worst prognosis of all genotypes. Note Vichinsky et al. does not use the term “balanced”, but rather “generally well balanced”. The 12% HbSS imbalance may have affected some of the results reported in the study, especially those that did *not* show statistically significant differences but only “positive trends”, such as vaso-occlusive crises (VOC) (**discussed in Item 2**)

Item 2: Table 5.12 Treatment Effects

ICER made an unusual decision to include a non-statistically-significant relative pain score of 0.868 as a legitimate positive “treatment effect” favoring voxelotor. Furthermore, despite a significant dose-response relating to Hemoglobin (Hb) in the 1500 mg versus 900 mg arms, there was no dose-response relating to VOCs. The 900 mg arm had per-person-year pain crises of 2.76, or 0.865 relative to placebo, versus a slightly worse 2.77 for the higher 1500 mg group, 0.868 relative to placebo. What is the rationale is there to view VOC difference between the 1500 mg and placebo arms as other than a statistical artifact? Also, as mentioned above, the 12% imbalance in HbSS genotype should be considered when evaluating treatment effect “positive trends”. Should the lack of statistical significant and dose-response at least be highlighted, with a rationale for using 0.868 given?

Item 3: Difference between hemoglobin and “hemoglobin-voxelotor complex”.

Voxelotor has been described as binding to the N-terminus of Hb alpha chain, creating conformation changes in Hb. It is unclear whether “hemoglobin” and “hemoglobin-voxelotor complex” should be used interchangeably. It is unclear to me how literature supporting the benefits of higher hemoglobin on the acute and chronic conditions cited in **Table 5.13** should be extrapolated to hemoglobin-voxelotor complex formed by treatment with voxelotor. Global Blood Therapeutics did not prove that Hb supplementation with hemoglobin-voxelotor complex has the same beneficial effects as supplementation with normal hemoglobin. Should this be highlighted and how should the potential drug effects shown in **Table 5.14** be interpreted with regard to voxelotor?

Thank you for your review and consideration

William Gerber
MPH, MBA, MS Accounting
Fairfield, CT

February 19, 2020
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,

On behalf of the Sickle Cell Disease (SCD) patients in the greater Kansas City Metro and State of Kansas, I am writing to express our concerns about the possible negative impact that your “Sickle Cell Disease: Draft Evidence Report” could have on our community and the care that patients receive.

For a disease that has been under-researched and had limited treatments available for nearly a century, I am concerned for the limitations that this report may have on access to valuable therapies for patients. I am happy that you have begun the research and dialogue on these therapies, but we question the “value” being placed on these therapies; especially when so few have previously been available to patients in the past.

There are so many unmeasured costs not present in the current form of the report. We also question the “value” being placed on the extension of life for SCD patients. How can a value be placed upon one’s life, whether it is a few years, or 50 years? As a SCD patient myself, I wonder how the valuation dialogue would be accepted by my mother, who has had three children all with SCD. Of those children, two are now deceased due to complications from the disease. If the current treatments were made available years ago, just the mere possibility of having her children present a few more years would be invaluable to her, as it would be for any other family impacted by this disease.

We ask that you strongly take into account this information and all unmeasured costs when finalizing the report and not impeding access of care to a patient population that has already endured much discrimination and lack of respect in the medical community.

Sincerely,

Kevin Wake
President
Uriel E. Owens Sickle Cell Disease Association of the Midwest

UNIVERSITY OF MINNESOTA

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Dr S D Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, 9th Floor
BOSTON MA 02109

Submitted via Email

Publiccomments@icer-review.org

20 February 2020

Dear Dr Pearson

PUBLIC COMMENTS ON SICKLE CELL DISEASE EVIDENCE REPORT: MODELING

As a professional health economist, with some 40 years experience, I have been concerned for some time with evidence standards and the lack of the standards of normal science in ICER modeled value frameworks. This applies more broadly to health technology assessment practices as advocated by groups such as ISPOR. I have published a number of commentaries on the lack of standards of normal science in the ICER value frameworks in the University of Minnesota journal *INNOVATIONS in Pharmacy* over the past 4 years¹. My latest commentary, published last Friday, considers your proposed 2020-2023 VAF².

Please find attached a list of questions that I and colleagues at the University of Minnesota have in regard to the modeling of imaginary worlds to support value claims in respect of sickle cell disease. I would appreciate your responses to the questions raised in respect of the sickle cell evidence report. We would appreciate a response to each question. As you will no doubt agree, meeting the standards of normal science for claims that are credible, evaluable and replicable is the foundation for the discovery of new facts; not the acceptance of assumption driven imaginary worlds which recycle 'known' facts.

A particular concern is the assumption by those developing cost per QALY lifetime models that the EQ-5D has interval measurement properties. It does not. The EQ-5D has only ordinal properties, it is a manifest scale, and should not be used to construct QALYs. Unfortunately, apart from the lack of scientific merit in constricting lifetime imaginary models, the misapplication of the EQ-3L utilities means

that your reference case model collapses. We note that Drummond et al in the last edition of their textbook maintain that the EQ-5D has interval properties ³. This is incorrect; their arguments are confused. I suggest the following references may assist you in exploring this question ^{4 5 6 7 8}. The issue is that the EQ-5D was not designed to have interval properties. If you want to attempt to demonstrate it has (*ex post facto*) then you need to show that for each disease state application (unidimensionality).

I note that your response to public comments are not released until the release of your final evidence report. As there has been some interest by colleagues, companies and others in the merits or otherwise of the ICER reference case VAF, these questions, as they are in the public domain, will be distributed. I am sure that they will be an issue at your Boston CEPAC meeting.

Would you please acknowledge receipt of these questions.

Sincerely

Paul C Langley Ph.D.
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**ICER: LONG TERM COST EFFECTIVENESS OF INTERVENTIONS FOR SICKLE CELL DISEASE:
 CRIZANLIZUMAB, VOXELOTOR, AND L-GLUTAMINE**

**PUBLIC COMMENT QUESTIONS: VALUE ASSESSMENT FRAMEWORK
 PLEASE RESPOND TO EACH QUESTION**

1. Model Choice	There are a large number of potentially competing models for the application of a reference case framework. Why did ICER choose this particular model framework (Section 5.1)?
2. Outcomes (1)	ICER points out (Section 5.1) that SCD ‘has a large impact on patient’s psychosocial wellbeing’. If this is the case why did ICER chose to model with the EQ-5D-3L system which only captures five symptoms with 3 response levels?

3. Outcomes (2)	Why did ICER utilize the EQ-5D-3L system when there are others to choose from, including the EQ-5D-5L (introduced in 2009) which is considered to be more sensitive in capturing responses?
4. Outcomes (3)	Given the number of alternative generic utility instruments why did not ICER caution readers that choice of an alternative system (e.g., EQ-5D-5L) could lead to different QALY measures?
5. Outcomes (4)	In early 2019 ISPOR published a good practice for outcomes research task force report (Brazier et al, <i>Value Health</i> 2019;22:367-75) for the identification, review and use of health state utilities for cost-effectiveness models. ICER appears to have ignored this practice recommendation. Why? Where is ICER's systematic review (pg. 70)? There is no reference to the Brazier paper.
6. Outcomes (5)	In respect of 5 (above) would ICER consider withdrawing its evidence report until a systematic review is presented to justify its choice of the EQ-5D-3L? If not, why not?
7. Outcomes (6)	Given ICER's choice of utilities for constructing QALYs, could ICER demonstrate from one or more empirical assessments that the EQ-5D-3L has interval fundamental measurement properties for the target SCD hypothetical population in its reference case modeling?
8. Outcomes (7)	In respect of 7 (above), if there is no evidence would it be reasonable to assume that ICER has simply assumed that the EQ-5D-3L for the hypothetical SCD has interval measurement properties?
9. Outcomes (8)	If the EQ-5D-3L for the target SCD population has only ordinal measurement properties, how would ICER justify constructing QALYs?
10. Outcomes (9)	In Table 5.16 presents utility estimates 'by assumption'. How does ICER justify this? Are they assumed to have interval measurement properties?
11. Outcomes (10)	In the report on oral semaglutide ICER introduced two separate utility systems (EQ-5D-3L and HUI Mk2) into its model? How can ICER justify this when the systems are quite different?
12. Imaginary Worlds	Is the reference case imaginary lifetime model intended to generate credible, evaluable and replicable claims for cost-effectiveness? If not, why not?
13. Imaginary Worlds	How much credibility should be attached to the ICER model when it is only one of many that could create imaginary claims in SCD for the products assessed? What sets the ICER model apart from others?
14. ISPOR: Approximate Information	In the 2018 ISPOR task force report on health Economics (Neumann et al, <i>Value Health</i> 2018;21:119-25) it is determined that economic evaluations are intended, not to test hypotheses, but to inform decision makers of the approximate value of interventions in terms of incremental cost-per-QALYs gained. Does ICER subscribe to this view?
15. ICER: Approximate Information	In respect of 14 (above) how would ICER define 'approximate value'?
16. ICER Approximate Information	How would ICER differentiate 'approximate information' from 'approximate disinformation'?
17. ICER Approximate Information	Where different utilities and model structures are presented in SCD lifetime modeled claims, how would ICER propose that their modeled

	'approximate information' is more 'approximate' than other modeled claims for 'approximate information'?
18. Lifetime Model	The ICER SCD model takes a lifetime perspective? How, therefore, are we to interpret the 'assumptions' driving this lifetime construct? Are they a 'realistic guess' or what?
19. Model Assumptions	ICER's models look to a future imaginary world for SCD intervention that extend decades into the future for a hypothetical SCD population. This relies on assumptions that have held in the past (from the literature), and are presumably assumed to hold into the future. Given Hume's induction problem, how does ICER justify a model built on assumptions?
20. Health Related Quality of Life Construct	ICER makes clear (to a certain extent) the difference between health related quality of life (HRQoL) and the broader concept of quality of life (QoL). In adopting the EQ-5D-3L as the utility measures, could ICER make clear as to what is the latent construct (if any) or other construct(s) that ICER is unable to provide this assurance, it should be made quite clear.
21. Rasch Measurement	It has been recognized since the 1960s (and in in health technology assessment since the 1990s) that if we are to capture the patient voice in therapy assessments we require a needs based QoL instrument to capture therapy impacts with interval measurement properties. Why has ICER continued to apply generic measures of HRQoL defended by what many see as a bogus population perspective argument? Could ICER provide their case for non-patient centric HRQoL measures?
22. Hypothetical Population	What is the case for modeling to create non-evaluable claims based on a hypothetical SCD population? Why was this particular population selected for creating the ICER imaginary lifetime SCD world? Does the EQ-5D have unidimensional interval scale properties for the target SCD population?
23. Multiplicative Assumption	In respect of 9 (above), if ICER cannot demonstrate that the EQ-5D-3L has interval properties, rather than ordinal, how does ICER justify the statement that HRQoL is multiplicative (Table 5.4)?
24. Assumptions	Why should we 'believe' ICER's assumptions as opposed to the assumptions underpinning competitor models?
25. Assumptions	Why should treatment effects from clinical trials be transferable to a reference case imaginary world?
26. Interval Scoring	In respect of the utility estimates in Table 5.16. Can ICER show that each of these has interval scoring properties (including the NICE report)? This applies also to the 'calculated' utilities.
27. Validation	Why has ICER ignored empirical validation (pg. 75) of claims?
28. Validation	In respect of 14 (above). Why has ICER sidestepped the question of empirical validation of the cost-effectiveness claims made in their reference case model?
29. Validation	Are any of ICERs claims in SCD capable of empirical assessment?
30. Base Case Results	Would ICER agree that if it cannot be demonstrated that the utilities for the hypothetical SCD population fail to demonstrate interval properties then the QALY base case results for the SCD products (Table

	5.22) are meaningless? [i.e., lifetime QALYs are a mathematically meaningless fabrication]
31. Thresholds	Would ICER agree that if it cannot demonstrate the integrity of lifetime cost-per-QALY claims (meeting fundamental measurement standards) then recommendations for pricing and affordability based on such claims are questionable?
32. Media Releases	Many companies have concerns that the media release ICER's recommendations for price discounting and affordability without detailing the model and its assumptions. Would ICER consider adding the following caution when its reports are released? <i>ICER wishes to emphasize that any conclusions and recommendations made in this report are specific to the model structure and its assumptions devised by ICER. Alternative models could be developed with their own structure and assumptions and come to possibly quite different conclusions and recommendations.</i>

REFERENCES

¹ <https://pubs.lib.umn.edu/index.php/innovations/section/view/formularyevaluations>

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⁴ Bond T, Fox C. *Applying the Rasch Model*. 3rd Ed. New York: Routledge, 2015

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⁷ McKenna S, Heaney A, Wilburn J et al. Measurement of patient reported outcomes 1: The search for the Holy Grail. *J Med Econ*. 2019;22(6):516-522

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A 501c3 community-based nonprofit organization | EIN: 47-2467018

Greetings Icer Review Board,

Today is a great day of hope! I am a mom of a child diagnosed with sickle cell disease. I can say today is great day of hope because as a mother watching her child experience many hard, devastating days battling complication for sickle cell disease, today I graciously watch my 17 year old son, Shamar thriving and happily joining his peers at school and accomplishing goals.

I am grateful for the simple opportunity of seeing my son enjoy more healthier days functioning much like his peers, hospital free and pain free experiencing less complications of sickle cell disease. Shamar has not always had the privilege of going to school with his peers. In fact, at the age of 8 years old, a normal school day and a routine appointment visit turned into our worst nightmare! On this day Shamar appeared healthy and was feeling fine, but his health quickly declined resulting in immediate admittance to the hospital and blood transfusion. Shamar was suddenly at risk for a stroke. Shamar's routine appointment alerted his medical team that his regular hemoglobin of a nine was a very abnormal six that declined within an hour to five. Upon his hospital admit, his hematologist later discovered the paro-virus & an aplastic crisis (shutting down the making of red blood cells) with associating sickle cell complications that caused intense pain at level ten all over which resulted in Shamar fighting for his life!

My son's journey has taught me just how fast sickle cell disease complications can impact one's life. This heredity hemoglobin disease starves organs of oxygen, slowly destroys organs, causes devastating pain episodes, declines one's health & impact a life of a patient & family, & causes uncertain days of life expectancy.

At 12 years old Shamar's health complications increased with challenges. Sickle Cell decided to be a beast, resulting to frequent hospitalizations & pain crisis lasting for a month. Going to school like his peers was no longer an option for Shamar. His education continued as a hospital homebound student. Imagine having to stay home battling severe pain as if someone is stabbing you repeatedly, experiencing frequent hospital stays & wanting to enjoy a normal student life like your peers & siblings. This change made Shamar express to me that he is not living his life. He felt sad & eager to attend school. I also gave up my job as a fulltime hospital social worker to care for my son. This was a difficult, but necessary decision which impacted our lifestyle and household income. My son needed my time, love & dedication. The hope of seeing his health improve meant the world to me. My son's hematologist discussed concern about Shamar's health and life expectancy. He discussed the need to consider a bone marrow transplant, monthly blood transfusions or medications (Hydroxurea & Endari). We decided to try Hydroxurea & Endari which truly has been a blessing for Shamar to experience a more normal life with a decrease of pain episodes and hospitalizations.



1701 W Wetherbee Rd. #771692 Orlando, FL 32877

Impacting Lives, Empowering Families & Giving Hope!

A 501c3 community-based nonprofit organization | EIN: 47-2467018

Shamar is now seventeen years old. Over his lifespan, my son has experienced over thirty Emergency Room visits & he has been admitted to the hospital sixteen times. The hospital admissions has lasted a minimum of seven days in the hospital and maximum of three weeks. Shamar's care requires countless appointments with specialist which include a hematologist, nephrologist, cardiologist, & pulmonologist. Annual test to monitor my son's health & Comprehensive care has helped my son. Since Shamar has been on Hydroxurea & Endari for the past three years, he has been hospitalized only three times for sickle cell complications. Shamar is a fulltime honor roll student that enjoys school, amusement parks, skateboarding and swimming. He is proudly in his school's assistant nursing program. He looks forward to becoming a certified nurse assistant and EMS technician. He plans to one day go college and become one of the best male Registered Nurses in history!

Our journey is one of many stories of families that have gained "Hope" to see our son survive and thrive with the help of present medications. As a mother and community advocate, Our community is in need of effective medications, hope & quality care. I have held the hand of parents that had to plan funerals for their child & I have seen too many RIP in our social media community. I was almost one of those parents. Medications are priceless when it comes to the life of a child and love one. Many sickle cell warriors are dying before the age of thirty. It is finally encouraging to know our community have treatment options present and on the rise. We are in a state of emergency for an increase treatment options. Our hope continues for quality care, access to treatments, increased treatment options and a universal cure.

Thank you for your time. I appreciate your investment to hear directly from patients and caregivers. I hope our journey offered some insight on the impact of sickle cell disease.

Respectfully Yours,

Carla Lewis

CEO & Founder of
Kids Conquering Sickle Cell
Disease Foundation, Inc.

Co-Founder & Director for the
Young Adult Sickle Cell Alliance
www.kidsconqueringscd.org



February 18, 2020
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,

On behalf of the approximately 400 Sickle Cell Disease (SCD) patients who are current clients of Martin Center Sickle Cell Initiative (MCSCI) in Indianapolis, Indiana, I am writing to express our concerns about the potential negative impact that your "Sickle Cell Disease: Draft Evidence Report" could have on our community.

As you stated repeatedly in your report, SCD is a multi-faceted condition that can cause extreme hardships on patients and their families. At MCSCI, we bear witness to these hardships daily. We see how SCD's impacts on patients vary dramatically from person to person but that they have multiple periods of severe pain in common. We see that they share other things to varying degrees, things like a life with uncertain length; lowered educational attainment levels, diminished economic opportunity; periods of depression and hopelessness; and so many other issues that have a negative effect on their quality of life. This begs us to ask the question, "how can anyone place an economic value on any of these things? Yet, it seems that this is what your report has the possibility of doing when viewed only on its surface.

We give you credit for confirming that the values of "...education, ability to work, the effect on caregivers and other costs" have societal benefits that the report has not yet measured. Yet, even though you acknowledge that "these additional societal benefits not currently included in the health care perspective are important for understanding the full potential impact of treatments and their value," the net effect of the report is that it still places negative values on the three therapies you analyzed. We are afraid that, after reviewing the report, payors whose only interest is in economics will likely be persuaded to be reluctant to cover these therapies and/or refuse to cover them altogether.

Your report summarizes that crizanlizumab has the potential to extend life by 2.4 years, that voxelotor could extend life by 2.1 years and the L-glutamine might extend life by approximately 1 year. We ask, "what is the value of those additional years to the patients, their families, their friends and their neighbors?" We think the answer is that the value is immeasurably higher than any one person or any one scientific analysis can quantify. It is our belief that any improvement in care and each gain in life quality, no matter how incremental they may be, is of significant value to every person affected by SCD. As a point of reference, I lost my wife of 12 years due to SCD complications in 1989 when she was only 36 years old. That was over 30 years ago but not a day goes by that I don't wish I could have had just a little more time with her.

That is why we urge you to more strongly consider the unmeasured costs of SCD before releasing your evidence report in March. At the very least, we urge you to more strongly emphasize the significant, immeasurable value of even small improvements in life expectancy, societal benefit and patient life quality.

Sincerely,

A handwritten signature in black ink, appearing to read "G. Gibson".

Gary A. Gibson
President/CEO

MY STORY AS A SICKLE CELL CARE GIVER

19th /February/2020

My name is Feddress. N. a 48 year old mother (Born 6th/April/.1971) to a 23 year old beautiful sickle cell girl (Born 8th /March/1996) .Am a Ugandan by Nationality.

I hold a diploma in Medical Laboratory Technology. I first qualified in this field at Certificate level at 25 years and as soon as I completed my training I was impregnated by my first boyfriend whom I first met at my secondary school.

I delivered my first baby girl and this gave me a lot of joy together with my boyfriend. When my baby was 7 months old she started falling sick .She could run very high temperatures and could swell both legs and feet crying with a lot of pain. We would buy some oils and massage to relieve the pain. Though I was already a medical worker I did not have the knowledge about the sickle cell disease.

One day when she run high temperature we took her to the Hospital where they tried to check for Malaria and it was not seen .We were referred to a National Referral Hospital for a sickle cell test which turned out positive. She was confirmed a sickle cell patient that day.

By that time the most worrying and feared disease was HIV and when I was told she had sickle cells it was like she had been diagnosed with HIV .This hurt me so much because I had too much love for my first baby. Little did I know that it would also disorganize our relationship!

Going back home with my boyfriend our love for each other reduced despite the counseling we got while we were given results. They explained to us that we both had the gene S which was inherited by our daughter (SS). As we shared the story to our relatives and friends they were advising us to leave each other and get new relationships.

Finally as she made 2 years of age, we separated and I was left with all the responsibility of taking care of my child. The father did not look back to support me .I suffered with the Hospital bills, the feeding and the school fees.

Since my child was sickly people named me the mother of a sickler .This hindered me from getting another serious partner and I ended up with no husband and hence one child in life.

I have really struggled a lot to bring up my child alone. Unfortunately by the time I got my baby my mother and Father had died. So my child would get admitted and we keep two in the Hospital with no support at all. At times I would be very block to the extent that I could not buy Food and enough drinks for my sick child. Paying Hospital bills was tag of war.

When I realized men could not marry me with my sickly child I decided to be a very good, committed and hardworking lady at place of work since my job was all. At times my girl could get sick and I request for my leave days to take care of her. Since I was a hardworking and committed lady I could not have any issues with my employers.

For me I never enjoy Annual leave days .I only reserve them for taking care of her when she falls sick. I have always lived in fear, fatigue, stressed with a lot of financial debts.

I have a big fear of my daughter developing a condition of surgery which needs millions of money, this is because she complains of a hip joint pain, which may even lead to a disability.

In order to do something out of my little earning in a country with poor economic status, I have always taken loans to build my home .In my life I have never got a full salary as the bank deducts the loan instalments. At times I take advances at work in order to pay Hospital bills. I have worked for four employers in life and my salary has never gone beyond 450\$ a month. I have got to use this money for everything.

My girl attended school at primary and secondary level but did not have opportunity to join University because she was on and off sick. When she completed secondary level she went to institution to do a course in Beauty and cosmetology but on completion she couldn't practice because of the chronic pain she developed in the hands due to arthritis.

My child has undergone several Hospital admissions, several transfusions especially from 16 years and above. From this age she would not take three months without a transfusion. With the many transfusions she started reacting to blood .One time she reacted badly to blood and almost lost her life. There are days when my child gets too much pain and the pain killers fail to work. At times she is managed on morphine pump.

Her condition also worsened when she was 21 years when she developed Rheumatoid Arthritis. The Hematologist suggested she had to get started on Hydroxyurea .She is now being managed by both Rheumatologist and Hematologist. At times we fail to keep appointments because of funds.

She was started on cocktail of drugs including Hydroxyurea, Hydroxychloroquine, Omeprazole, prednisolone, folic acid, Celecoxib, Aceclofenac. These drugs are also bought when I have the money but at times she misses them when am block.

Despite all these expensive drugs she still faces painful crisis and gets anemia. These many drugs are exposing her to bad side effects .Arthritis has started deforming her. Anyway to mention but a few.

I would be glad if there is an alternative care to do away with the pains that the sickle cell patients experience.

Yours, Sickle cell Care Giver

Feddress .N.

Tel.256-772370078 or 256-701370078

Email: zakifed@yahoo.co.uk

MY STORY AS A SICKLE CELL PATIENT

20/February/2020

My name is Nanyondo Matilda, a Ugandan by Nationality, 23 years old battling with sickle cell anemia and Arthritis. I was diagnosed at 7 months of age.

My mother told me it was one day at that age that I had very high temperatures. They checked my blood, the malaria was not there. The laboratory Technician at Nsambya Hospital saw features that pointed to sickle cell, as he checked the blood slides.

He suggested to my mother to go for a confirmatory test at Mulago hospital. When the test was done it was confirmed to have Sickle cell Disease. My mother said her blood and that of my father was taken. My mother was found to have HBAS, my Father was HBAS and my blood was found to have HBSS.

I was told this confused my parents a lot. Because they were having many advisors on that same issue and that led to break up of their relationship when I was only 2 years old. My mother struggled to educate me and pay for medical bills as I was sickly. What I remember was she took me to only good schools but only that I used to be sickly that I did not achieve my dreams.

At my first primary school, I used to be described as the yellow-eyed girl. I would be called the girl with a big tummy. One day one of the girls asked me whether I had sickle cell and I denied but later I heard it from her friends and I was very sad about it. At school, most children would ignore me because they feared me getting into sickle cell crisis. I had very few friends at school because of my condition. To make it worse even teachers would ignore me and talk ill about me. The moment my mother took me to a new school she would sensitize all teachers about my condition but this would make people say am naughty.

To assure you it's not easy to be confident with this disease I have lived with low self-esteem yet I was a bright girl. I remember very well the stress my mother has gone through to bring me up single handedly. Me being her firstborn to assure you it affected her marriage life.

I have been on and off sick but I had transfusions from 16 years up-to-date. At 21 years I had several transfusions until a hematologist prescribed Hydroxyurea. Still at the same year I developed another condition called Arthritis. Am now attending a specialized clinic and see a Rheumatologist. This condition worsened my life because I have to take painkillers every day, take hydroxychloroquine, Hydroxyurea, folic acid, aceclofenac, Omeprazole, and all these drugs are very expensive yet my mother cares for me alone. In addition to that my mother has got to feed me, pay for the house helper who takes care of me.

With arthritis the pain am going through is terrible, I lost some activities. I can't wash, can't clean the house, generally my life changed no more energy in my hands. As you know hospital attendance is not easy as you reach hospitals there many issues you get there. Issues like no drugs, not enough workers, no good toilets it all adds to ill health stress.

What hurts me most I did not have opportunity to do good courses that would get me good job to support my mother who has suffered with me I still depend on the little she earns.

I would be happy together with other Ugandan patients if new drugs are discovered to reduce the stress, and agony that we go through as a result of sickle cell disease.

Yours Sickle cell patient,
Nanyondo Matilda
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Email: matilda.nanyondo@yahoo.com

Comments on ICER’s Draft Evidence Report, “Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value”

February 20, 2020

INTRODUCTION

Novartis would like to thank ICER for the opportunity to provide input on its draft evidence report “Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value for new treatments for sickle cell disease (SCD).” Novartis is committed to improving the lives of those who suffer from SCD, a disease with a high burden and unmet need, and few effective treatment options. SCD causes an extensive range of acute and chronic complications and organ damage, ultimately leading to early mortality.¹⁻³ SCD also significantly diminishes patients’ quality of life (QoL).¹ Vaso-occlusive pain crises (VOCs) are the hallmark of SCD and are the primary cause of hospitalization and emergency department use among patients with SCD.² These acute, unpredictable, and excruciating painful events cause many patients to live in a state of fear and anxiety, making normal life nearly impossible, and causing enormous psychosocial distress.^{2,4-6} The SUSTAIN clinical trial showed that Adakveo (crizanlizumab-tmca) reduced the rate of VOCs by 45.3%.⁷ Adakveo is a new treatment that has demonstrated meaningful benefits to individuals with SCD in more than 20 years.⁸

Novartis acknowledges ICER’s extensive efforts to document, and attempt to account for, the pivotal experiences of US patients living with SCD in their draft report. First, Novartis applauds ICER’s assessment of the clinical effectiveness of Adakveo, indicating that there was “adequate certainty that crizanlizumab will provide a positive net health benefit.”⁹ Second, Novartis acknowledges ICER’s effort to describe, through both patient narratives and fielding a *de-novo* survey, the extraordinary burden sustained by patients with SCD. As Section 2 of ICER’s draft report meticulously documents, not only do patients with SCD have shorter life expectancy than the general public, but they also face in SCD an all-encompassing condition, which imposes severe limitations on daily personal, work and family life for both patients and their caregivers. Importantly, patients with SCD face social stigma and racial bias-related barriers in accessing timely and appropriate healthcare.

Novartis commends ICER for analytically distinguishing and describing various important components of the burden of SCD, but cautions that ascribing (and calibrating) modeling inputs for this multiplex interplay of difficult-to-measure value components is deeply problematic and poses significant methodological challenges. Thus, despite commendable efforts by ICER, estimating the value of new treatments in SCD in the US via cost-effectiveness analysis remains extremely challenging. We have outlined nine recommendations for ICER to consider when revising its draft evidence report.

CHALLENGES SURROUNDING COST-EFFECTIVENESS ANALYSIS IN SICKLE CELL DISEASE IN THE UNITED STATES (US)

Cost-effectiveness analysis (CEA) is a well-known approach to measuring the value of new health interventions. Within this approach, The Second Panel on Cost Effectiveness in Health and Medicine recommended measuring health effects in quality-adjusted life years (QALYs).¹⁰ Despite this recommendation, measuring the value of new SCD treatments is particularly challenging for both contextual and technical reasons. Admittedly, ICER acknowledges many of these limitations within their draft report. In Section 5.1 of the draft report,⁹ for instance, ICER notes that it is not possible to capture the full psychosocial impact of systemic issues, such as racism.⁹

The technical limitations of CEA in SCD include inconsistent evidence and an evolving understanding of SCD’s wide-ranging and complex impacts.

In addition to these technical limitations, there is no consensus on, and no validated methods exist for quantifying the value of other important aspects (e.g., potentially reducing inequality, impact on family planning decisions).

OVERVIEW

Modelling the value of Adakveo using a CEA model in the US is particularly problematic for the reasons described in the table below.

Table 1: Overview of limitations of CEA modeling for Adakveo (crizanlizumab-tmca)

Category	Critique
Key evidence limitations	<ol style="list-style-type: none"> 1. The overall benefit of reducing VOCs is not fully captured in ICER’s model, as critical evidence is evolving 2. ICER should use the average weight of the patients in the SUSTAIN randomized clinical trial when calculating the cost of treatment with Adakveo
QALY-based CEA models fail to measure the full impact of SCD	<ol style="list-style-type: none"> 3. QALYs underestimate the short-lived but intense experiences such as VOCs and therefore undervalue the beneficial impact of Adakveo 4. Society places a high value on health gains for patients with severe disease 5. Society values health gains more if they reduce inequality
Traditional CEA fails to account for wider social and economic impacts of SCD treatment	<ol style="list-style-type: none"> 6. SCD has a significant negative impact on family and marriage decisions 7. The debilitating physical effects of SCD inhibit educational achievement, limit career opportunities and development, and earning potential 8. SCD entails significant caregiver and family burden 9. The lack of alternative treatment options means that patients with SCD have above-average opioid exposure and consequent risk of dependence

EVIDENCE SUPPORTING AFOREMENTIONED LIMITATIONS

1. The overall benefit of reducing VOCs is not fully captured in ICER's model, as critical evidence is evolving

SCD substantially shapes patients' daily lives, including emotional and physical wellbeing, relationships, education, and work.¹¹ VOCs are the hallmark of SCD.² In a recent global survey, patients with SCD experienced an average of 5.2 VOCs per year, resulting in frequent hospitalization.¹¹ Yet pain is difficult to measure; in fact, there are no objective diagnostic tests for measuring VOCs, as a clinical diagnosis is required.^{12,13} Research presented during the American Society of Hematology (ASH) 2019 Annual Meeting shows that the QoL of patients with SCD measured in the form of utility is 20% lower during a VOC compared to previous estimates¹⁴, (i.e., utility during crisis is 0.311 in recent research¹⁴ vs. previous estimate of 0.39 from Anie et al. [2012]¹⁵).

2. ICER should use the average weight of the patients in the SUSTAIN randomized clinical trial when calculating the cost of treatment with Adakveo

The mean weight from the crizanlizumab 5mg/kg arm of SUSTAIN trial (69.46 kg)¹⁶ should be used to estimate the number of doses of Adakveo, and consequently, the cost of treatment with Adakveo. Instead, the ICER draft report appears to use a general-population weight for dosing and cost of treatment calculations; however, patients with SCD typically weigh less than the general population. For example, a real-world study of patients at the Montefiore Medical Center in New York found, that the average weight of a patient with SCD was 61.0 kg for patients aged 21-30 and 63.7 kg for patients aged ≥ 40 years.¹⁷ Further, given the ages of patients in the SUSTAIN trial (16 to 63 years of age),⁷ their mean weight should inform the assumption of the cost of treatment with Adakveo for the majority of patients with SCD in the real world in the US. Basing treatment dosing on more realistic weight assumptions is needed to accurately calculate the dosing and cost of treatment with Adakveo in the real world.

QALY-BASED CEA MODELS FAIL TO MEASURE THE FULL IMPACT OF SCD

3. QALYs underestimate the short-lived but intense experiences such as VOCs and therefore undervalue the beneficial impact of Adakveo

While quality-adjusted life years (QALYs) are a useful metric for CEAs in other disease areas, the Second Panel on Cost Effectiveness in Medicine notes that: "QALYs may not accurately reflect the burden of short-lived but intense experiences. Thus the benefits of interventions that reduce the incidence of such experiences may be undervalued."¹⁰ Clearly, VOCs fall into this category.

4. Society places a high value on health gains for patients with severe disease

People are willing to give up aggregate health to give priority to patients with more severe disease that have a significant impact on patient QoL.¹⁸ Governments and health policy bodies in some European countries have started to incorporate considerations based on disease severity and small patient populations into their guidelines for evaluation of new technologies.¹⁸ Differences in how such factors are accounted for lead to wide variation in value estimates across international HTA agencies.¹⁹

5. Society values health gains more if they reduce inequality

Society values QALY gains more if the treatments also reduce inequality.²⁰ However, measuring the value of improved health equity is challenging due to the wide scope and lack of agreed upon normative framework.²¹

In the US, the burden of SCD is borne primarily by ethnic minorities, particularly African Americans.²² In addition, a majority of adult patients with SCD are in the lowest income quartile²³ and are covered by Medicaid,²⁴ as the debilitating symptoms of SCD can make finding and retaining employment difficult.^{25,26} Subsequently, patients with SCD and their families tend to have lower incomes.²³ Further, 31.1% of US physicians are not accepting new Medicaid patients,²⁷ and studies have shown that patients with SCD covered by Medicaid may have less access to health care and receive lower quality care.^{28,29} These factors combine to exacerbate disparities in health care for patients with SCD.²⁹

TRADITIONAL CEA FAILS TO ACCOUNT FOR WIDER SOCIAL AND ECONOMIC IMPACTS OF SCD TREATMENT

Typical CEA studies do not consider a variety of important benefits, whether due to measurement difficulties, or a narrowly defined perspective.^{30,31} SCD has particularly wide debilitating impacts on patients that are not captured by traditional CEA.

6. SCD has a significant negative impact on family and marriage decisions

As ICER has noted, “Some patients and family members described making decisions to avoid marriage to maintain health insurance or forego having children to avoid passing on the gene to the next generation.”³² Quantifying how Adakveo would affect these decisions and the value of any changes in decisions is difficult, and accounting for such in CEA is challenging.

7. The debilitating physical effects of SCD inhibit educational achievement, limit career opportunities, development, and earning potential

Productivity costs are the most frequently included indirect cost in CEA.^{30,31} Recent research has shown that patients with SCD have substantially lower lifetime earnings compared to similar individuals without SCD.³³ SCD in general and VOCs specifically are associated with work productivity impairment and impact patients’ ability to participate and remain in the workforce. In the US, patients with increased frequency and severity of VOCs reported significantly greater absenteeism and overall productivity loss.²⁵ Patients with SCD with ≥ 4 VOCs have a 47% chance of applying for disability compared to only 12% for patients with SCD with 0 VOCs.³⁴ Despite a desire to work, patients with SCD have high rates of unemployment. SCD can prevent individuals from completing their education and advancing in their career.²⁶ Moreover, ICER has noted that some caregivers leave the workforce to provide care, resulting in additional economic costs.⁹

8. SCD entails significant caregiver and family burden

The chronic pain caused by SCD may lead to emotional and behavioral changes that affect the lives of family members, friends, and colleagues.^{35,36} Caring for a person with chronic pain can lead caregivers to experience physical and psychological health impairments, decreased relationship satisfaction, and lower QoL.³⁷

Studies of caregivers of children with SCD found they suffer from disease-related parenting stress and have significantly higher depressive mood scores.^{38,39} While parents are typically the

caregivers for children with SCD, for adults with SCD, caregivers may be spouses, relatives or friends, whose burden may be underestimated in ICER's model.

9. The lack of alternative treatment options means that patients with SCD have above-average opioid exposure and consequent risk of dependence

Due to acute and chronic pain, patients with SCD are frequently exposed to opioids.^{40,41} In a study of Texas Medicaid recipients, 58.7% of patients with SCD had ≥ 1 opioid prescription, with a mean of 4.2 prescriptions over a 12-month period. Multivariate analysis examining the relationship between VOC events and opioid use reported that for every increase in VOC event, the number of opioid claims increased by 9.5% (incidence rate ratio = 1.095; 95% CI, 1.078–1.111; $P < 0.0001$).⁴⁰ Another study found that 65% to 70% of Medicaid recipients with SCD and 54% to 57% of commercial insurance-covered patients with SCD had an opioid prescription in a given year.⁴¹

While patients with SCD are not at increased risk of opioid pain reliever-related death compared to opioid users with other diseases,⁴² those individuals who do abuse opioids can impose substantive direct and indirect costs.⁴³

CLOSING REMARKS

Novartis recognizes the need for a holistic, evidence-driven approach to determining the value of new treatments, which incorporates clinical outcomes, patient experiences, benefits to the healthcare system, and societal value. We are confident in the value that Adakveo brings to patients with SCD, as well as society, particularly through the significant reduction of VOC, which is the hallmark of the disease. Novartis commends ICER for the extensive efforts to index individual determinants of the value of Adakveo, and quantify their complex interplay. However, we note that there continue to remain significant methodological challenges for estimating the value of new treatments in SCD in the US via CEA, challenges which we consider substantial at this time within the CEA framework.

Sincerely,

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APPENDIX

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February 20, 2020

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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 regarding treatments for Sickle Cell Disease (SCD). SCD is a debilitating disease impacting roughly 100,000 individuals in the United States¹ and disproportionately affects racial minorities. African-Americans are particularly at risk, with SCD occurring approximately one in every 365 births. Despite the description of the disease first being formalized in 1910, there has been limited innovation for the disease until very recently. With this in mind, it is imperative that ICER act responsibly in its assessment to avoid the consequence of limiting treatments to a population that is in great need of them. PIPC encourages ICER to give serious consideration to the following comments.

The QALY is a Particularly Inappropriate Metric to Evaluate Treatments for SCD

PIPC has highlighted the discriminatory nature of the QALY, as well as the limitations of the metric as a measure of health gain, in many previous comments on ICER assessments. Given the complex nature of SCD, its severity, and the fact that the burden disproportionately falls upon specific groups within society, the QALY is a particularly inappropriate method for evaluating any value accrued from interventions aimed at its alleviation.²

Numerous studies have highlighted how key factors such as severity of disease,³ pain levels, and sparse availability and limited effectiveness of alternative treatments — all relevant for SCD — are considered as key determinants of priority in health care settings.^{4,5} In fact, some health technology assessment

¹ Sickle Cell Disease Coalition. About Sickle Cell Disease. Accessed February 19, 2020.

² Levenson JL, McClish DK, Dahman BA, Bovbjerg VE, Citero VD, Penberthy LT, Aisiku IP, Roberts JD, Roseff SD, Smith WR. Depression and anxiety in adults with sickle cell disease: the PiSCES project. *Psychosomatic medicine*. 2008 Feb 1;70(2):192-6.

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⁵ Gu Y, Lancsar E, Ghijben P, Butler JR, Donaldson C. Attributes and weights in health care priority setting: a systematic review of what counts and to what extent. *Social Science & Medicine*. 2015 Dec 1;146:41-52.

systems in European countries such as Norway, Sweden and the Netherlands⁶ actively use information on these factors to inform approval decisions for new medicines, given the limitations and simplicity of the QALY as a measure of health gain.

Additionally, health state valuation studies that translate into QALYs are undertaken in predominantly white populations, and weighting calculations are largely constructed using linear regression which over-homogenizes weights around the mean. The selection and construction of the ‘domains’ that make up quality of life tools were constructed by a small group of white men twenty years ago in Switzerland.⁷ No one has challenged these sets to be updated, as it would be inconvenient for the method, but it is very clear that this type of metric is highly inappropriate for ICER to use in evaluating a treatment for a disease that disproportionately impacts people of African and Hispanic descent.

If access and approval decisions around new healthcare technologies are made based on metrics that treat patients as averages like the QALY, and these averages are driven by regression towards majority populations, minorities within the population will ultimately suffer the most.

Standard of Care is a Faulty Comparator, as it Does Not Truly Exist for SCD

ICER chooses to use the comparator of “usual care,” which is neither standardized nor considered comprehensive care for SCD. SCD is a syndrome of diseases and care for any two patients can look markedly different depending on disease subtypes and the unique complications experienced by each patient. ICER even acknowledges in its report that “baseline or usual care for patients with SCD is highly variable and represents a failure in the US health care system.” Despite this recognition, ICER continues to utilize methods that do not adequately account for this variability.

SCD patients are a largely underserved population. There is a lack of specialists and clinicians with expertise to treat SCD, leading patients to seek care from generalists who are often not equipped to help patients manage their disease. Due to the lack of standardized care for SCD, treatment plans administered by generalists often vary drastically depending on the unique characteristics of each patient. Furthermore, non-specialists also often assume SCD is a pain condition, which can lead to inappropriate treatment for the disease’s complications.

ICER Chooses to Use Claims Data Instead of Listening to Input on Standards of Care from Patient and Clinician Stakeholders

ICER’s report uses claims data to determine the number of acute pain crises (APC) in SCD patients. Administrative and accounting data sets such as claims data sets have the advantage of being real-world data that are more likely to reflect ‘actual’ cost data than the more traditional ingredients approach.

⁶ Angelis A, Lange A, Kanavos P. Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. *The European Journal of Health Economics*. 2018 Jan 1;19(1):123-52.

⁷ Oliver A. *Discovering the QALY: Or How Rachel Rosser Changed My Life*. Alan Williams in *Personal Histories in Health Research*, ed. Adam Oliver. Nuffield Twst. London 2005.

Nevertheless, there are many variables for which administrative data are noted as being poor proxies. Data not reflecting service over- or underutilization and ineffective coding procedures are common flaws in administrative data.^{8,9,10}

This issue holds particularly true in evaluating APC for SCD. When you speak to SCD patients or clinicians they will tell you that the standard of care is to handle most APC in a home setting, not through hospital admission. The American Society of Hematology (ASH) noted this to ICER in its first comment letter, stating that “many patients manage both their acute pain and chronic pain at home. Adequate management of acute and chronic pain associated with SCD is an ongoing challenge both for patients and the clinicians responsible for their care.” This assertion from the patient and clinician community is backed up by studies that show patients managed the majority of their APC at home versus in a hospital setting.¹¹ With this in mind, claims data will drastically underestimate the typical prevalence of APC events for SCD patients.

The Assessment Fails to Capture Outcomes that Truly Matter to SCD Patients.

As is typical in ICER assessments, both of the trials undertaken to evaluate quality of life effects and the studies from which the model utilities are sourced were undertaken using generic patient-reported outcome (PRO) tools, the EQ5D and the SF36, rather than disease specific tools.

SCD carries a large disease burden that is not adequately captured using generic PRO tools. As a group of SCD stakeholders shared with ICER in their initial letter, “[t]he debilitating nature of SCD impacts social relationships, employment, and the educational attainment goals of patients....Likewise, there are notable financial and emotional burdens on the caregivers and families of patients with SCD.” Given the massive disease burden of SCD, specific PROs should have been used and an attempt should have been made to capture other cost factors — hospitalization, lost productivity, caregiver burden, etc. — in the base case, not just the contextual considerations.

There have been numerous studies suggesting that generic PRO tools such as EQ5D are poor at measuring marginal changes in quality of life effects across health states,¹² and that they are particularly

⁸ Whittle J, Steinberg EP, Anderson GF, Herbert R. Accuracy of Medicare claims data for estimation of cancer incidence and resection rates among elderly Americans. *Medical care*. 1991 Dec 1:1226-36.

⁹ Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, Kadri SS, Angus DC, Danner RL, Fiore AE, Jernigan JA. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. *Jama*. 2017 Oct 3;318(13):1241-9.

¹⁰ Abbas S, Ihle P, Köster I, Schubert I. Estimation of Disease Incidence in Claims Data Dependent on the Length of Follow-Up: A Methodological Approach. *Health services research*. 2012 Apr;47(2):746-55.

¹¹ Smith WR, Penberthy LT, Bovbjerg VE, McClish DK, Roberts JD, Dahman B, Aisiku IP, Levenson JL, Roseff SD. Daily assessment of pain in adults with sickle cell disease. *Annals of internal medicine*. 2008 Jan 15;148(2):94-101.

¹² Payakachat N, Ali MM, Tilford JM. Can The EQ-5D Detect Meaningful Change? A Systematic Review. *Pharmacoeconomics*. 2015;33:1137–1154.

poor measures of quality of life in SCD.¹³ This brings us back to our previous point about the QALY. It is imperative when evaluating treatments for a disease as complex as SCD that disease-specific metrics are used.

ICER Makes Faulty Assumptions About Lifetime Cost of Treatment

ICER's model makes the assumption that patients will be using these new drugs under optimal prescribing conditions non-stop from the age of 24 years through to death. This is highly unrealistic.¹⁴ It is typical in drugs taken for chronic conditions for patients to take treatment holidays, often when the treatment is effective, and at times when it is ineffective, as agreed by their physicians.¹⁵ It is also true that drug use — especially of specialized drugs — falls away later in life when pain relief and symptom management become more common. In addition, ICER assumes that the price of these treatments will remain the same for the next 20 years, which is very unlikely.¹⁶ What is more likely is that generic substitutes will enter the market, driving down prices. If you factor in this steep drop in price after 10-15 years, ICER's cost estimates would drop dramatically. ICER also does not factor in savings from reducing the incidence of expensive hospital care, which would impact the assumed lifetime cost of treatment.

Conclusion

ICER risks doing the SCD community a disservice by using the QALY, a metric highly inappropriate for the assessment of SCD treatments, and by failing to listen to the community about factors like standard of care and outcomes that matter to patients that should be meaningfully incorporated into its model. We strongly encourage ICER to listen closely to the SCD community and amend its model accordingly.

Sincerely,



Tony Coelho
Chairman
Partnership to Improve Patient Care

¹³ Keller S, Yang M, Treadwell MJ, Hassell KL. Sensitivity of alternative measures of functioning and wellbeing for adults with sickle cell disease: comparison of PROMIS® to ASCQ-MeSM. Health and quality of life outcomes. 2017 Dec;15(1):117.

¹⁴ Abrahamowicz M, Tamblyn R. Drug utilization patterns. Wiley StatsRef: Statistics Reference Online. 2014 Apr 14.

¹⁵ Alpert A. The anticipatory effects of Medicare Part D on drug utilization. Journal of health economics. 2016 Sep 1;49:28-45.

¹⁶ Lichtenberg FR, Duflos G. The effect of patent expiration on US drug prices, marketing, and utilization by the public. Manhattan Institute for Policy Research. 2009.

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Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Tisha A.

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

My name is Tisha, I'm 27 years old and I live in Georgia.

Please discuss your SCD Story:

I was diagnosed with Sickle Cell (SS) when I was two weeks old so I've been dealing with it my entire life. When I'm having a crisis it feels like someone is stabbing me constantly and a lot of the time I can't move. I experience pain almost everyday. I try not to let it affect my everyday life, Thankfully I'm still able to work but I will say it is hard having to deal with the constant pain.

Please discuss any experience with chronic pain:

If I had to describe my pain in a few words, I would say it's a stabbing pain that I get in my legs, knees and lower back. Sometimes it can last for a few hours or sometimes it can last for a few days. If I'm stressed out about something then I will most likely have pain, but a lot of the times when the weather changes I get sick. Usually the rain is what makes me really sick and puts me in the hospital.

Please discuss any experience with management of sickle cell pain at home:

I typically manage my pain at home. I'm not really a fan of going to the hospital. When I am at home I take my pain medication as well as my other medications (hydroxyurea, folic acid, etc) I also make sure that I cover up. And I drink plenty of water. I typically don't go to the hospital every time I have a crisis but I have had over 20 crises in the past year and I have maybe been to the hospital about 12 times. I tend to not go to the hospital when I'm sick because I work a full time job, or I do not want to stress my caregiver. But most of the time I do not want to go to the hospital because going to the ER gives me anxiety sometimes I am not treated the best or the do not believe that I am sick.

Please discuss any experience with fatigue:

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

I get fatigued quite often. At least twice a week. Usually My body is just really tired and I will sleep the entire day away.

Please discuss any experience with other complications:

Yes, I have a lot of anxiety because of my sickle cell I never really know when I'm going to get sick so it makes me anxious. I also suffer from some suicidal thoughts.

Please discuss the unmeasured costs of sickle cell disease:

Sometimes I have to miss days of work at a time, my caregiver also has to miss days from work when I'm sick to make sure that I am getting the proper treatment

Please discuss the impact of stigma and discrimination:

Most people don't believe me when I tell them that I have sickle cell. They say "You don't look sick." Most people don't even know what it is. Some doctors and nurses don't believe me when I tell them I'm in pain. I feel as though I have to prove to other people that I am sick. Sometimes I feel as though they think I am a drug seeker and I am not. I am also a black woman and I do feel as though that has a lot to do with it.

Sincerely,
Tisha
allentisha56@yahoo.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Georgene Glass

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Family member or Caregiver in the sickle cell disease community.

Briefly introduce yourself:

My name is Georgene ``Gina" Glass ,I am the mother of two with a 4 year old Gia,that has Sickle Cell Disease (SS). I am also the founder of Dreamsickle Kids Foundation, the first Sickle Cell Organization in the state of Nevada, and also a Community Health Worker. I have some other credentials that may lend credibility to what I say but I'm most proud of those titles I have earned because of Sickle Cell Disease.

Please discuss your SCD Story:

I was told when my oldest child was about 6 ,that I couldn't have more children. It stung at first but as the years went by and became a mother at 18. I grew to accept this fate. I knew my partner had the SCT, I had forgotten I also carried it and believing I could not have Kids, it was never a second thought. In September of 2014 after 13 years of being a mother of one, I was pregnant. Confused as to what I would do. I was more scared of being pregnant at 31 with an established career than when I was 18 , fresh out of high school and a single parent. Around 4 months gestation I had routine testing done and was told I carried the SCT and my child's father needed to be tested. I advised he knows he is a carrier and they tested him anyway and sent us to speak with a geneticist. After it was explained that we had a 25% chance of having a child with SCD, by this time I'm almost 6 months pregnant and the doctor then advised if I wish to terminate I have two weeks to make the decision because of how far along I was. By this time I felt movement, started thinking of names, how she would look. I am not good at math and didn't know much about SCD, but 25% did not seem such a risk to have an abortion. I had my baby and a few weeks later her doctor called to confirm the newborn screening showed she did have SCD. I didn't know how to react. I felt sad, I felt guilty for giving this to her, guilty for being irresponsible, guilty that now I would have to take more time away from my oldest child that already had no father because I would have to deal with a `sick " child. I began to prepare for what may be her fate. We relocated from the pricey Orange County California to Nevada. I took a job with a well known insurance company, with the job came a steep pay cut ,but the cost of living seemed to make up for it. Gia went over a year with no complications. In September of 2016, she came down with pneumonia. I took her to the hospital around the corner from home, a

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease Patient Advocate Responses

new fancy hospital, they gave her tylenol for the fever and an antibiotic shot and sent her home. Over the next few days she did not get better, one night I could hear her struggling to breathe. I immediately googled a hospital in a more urban area with the hope's they would be more familiar with SCD. I drove 40 minutes and after I disclosed her diagnosis and her symptoms, the staff immediately took her stats, got her an x-ray. The doctor stated she has pneumonia in both lungs and would be going to ICU. That was the scariest time in my life. She then got sick in February of 2017, the week before I was to start my job with my new employer. I separated from my job of over a decade and had no insurance. I always worked so I didn't even know how to apply for Medicaid. My hospital stay in February cost me 21000, which of course went on my credit. After starting my job, Gia was sick multiple times, I willed myself to hang on for the 12 months to get FMLA. The company I worked for which was 100 years old never heard of SCD until me. I managed to keep my job and get FMLA. Because of their inexperience with SCD, it became clear my bosses didn't really believe I needed the time off for my sick child, after all desk photos and social media showed her looking just fine. March 1st my FMLA went into effect. By May 30th I was terminated for attendance on a technicality with my FMLA and the time the doctor had put for me to have off I had exceeded that because I can't tell SCD to stop so I can go to work. Now I became a single mother of two that had to apply for Medicaid and get food stamps to be able to feed my children in a state that because of no state taxes does not have adequate resources for those who fall on hard times. I went from making almost 6 figures to food stamps in less than 2 years. While the foundation I created in the state continues to excel, I am getting eviction notices from paying my rent late every other month. I have a child graduating high school with good grades and because of the financial position I am in. I can not even celebrate her as I planned to. The stress that raising a child with a genetic rare Disease puts on you is unimaginable. I worry about how I will provide for my children. I worry if the doctor she gets on each emergency visit will care or just dismiss us because of SCD or even our race. I have to make sure that I react and behave a certain way in hospital settings so that the treatment my child gets is not adversely affected. Even if I am justified in expressing frustration, not just because of the stereotypes of the disease but the racial bias. I am not so naive, that I don't know that as a black woman expressing my disdain publically is viewed differently than if a white woman were to express the same thing. I am teaching my child at 4 to be more respectful of medical professionals than anyone else because your life depends sometimes on how they feel about you. I go into those settings minimizing what I know because I don't want to bruise the ego of that doctor or nurse. There are many things you have to worry about when you go to a hospital as a black person and a person with SCD. All one should be concerned with is getting help not if you look and talk in a way to be respected and not dismissed.

Please discuss any experience with chronic pain:

My daughter gets SCD pain mostly in her back. Recently she had pain for almost a month and spent 5 days in the hospital with pain and the flu. This year she is supposed to enter Kindergarten and I am scared and trying to figure out a way to homeschool. Germs are a big fear, but teachers thinking she is being insubordinate because she's in pain, or cold, or has frequent bathroom trips from drink excess water

Please discuss any experience with management of sickle cell pain at home:

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

We manage pain at home with a heating pad, lots of hydration, over the counter children's medications Tylenol and motrin, and prescription hydrocodone.

Please discuss any experience with fatigue:

My 4 yr old can only run so long much less than other children her age. It makes me feel bad because she has so much energy but physically she can not keep up.

Please discuss any experience with other complications:

Most other complications that she has experienced are frequent pneumonia and Acute Chest Syndrome.

Please discuss the unmeasured costs of sickle cell disease:

We have finally invested in a water dispenser as Gia drinks so much water. Supplements can range from \$8 a bottle to \$150 for a 3 month supply of a multi pack. Gia has to eat a more specialized diet as we are learning too much cheese or cream causes her to go into crisis. Last month ,we spent about \$600 on food and supplements just for Gias needs.because of mounting medical Bill's for Gias SCD, my credit is taking a dive, if my lease is not renewed in June , not sure what place would accept us as a tenant with my poor credit.

Please discuss the impact of stigma and discrimination:

The stigma SCD patients get from having bad attitudes,being a drug seeker and complaining are things that I work to not have associated with my daughter when she gets older. Race plays a major part in how medical professionals treat SCD patients especially if you're of African descent. Personally I watched my previous employer give a woman with a sick child of another race who did not yet qualify for FMLA every concession to be there for her child and not have her absences negativity affect her employment. But myself that qualified for FMLA they found a technicality in my FMLA and terminated me. So you get discriminated against because of your disease and people assume it's not that big a deal or painful and then for being black.

Please discuss the impact of hospitalizations:

To go a full year with no hospitalization would be a blessing. It is hard being in the hospital and seeing her get poked and prodded. It is also lonely, I could never again leave her there alone. I can't even focus on getting a job because I worry if she has to get hospitalized I would lose it. I can not get much done when she is hospitalized. I leave my 17 year old to fend for herself. It has to be hard to go from the only child for over a decade to a sister of a child with a disability and now all focus seems to be on the new kid. Makes me feel like a horrible mother.

Please provide any comments about the current or new treatments for sickle cell:

Gia has only tried Endari so far, we have experienced no side effects in the 3 months she's been using. My family and I believe it gives her more energy and her hemoglobin seems to stay at 8 before it was high 6 to mid 7 but never 8 consistently.

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Sincerely,
Georgene Glass

Ginaglass@dreamsicklekids.org

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Daryl Rosborough

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

My name is Daryl Rosborough and I have Sickle Cell SS. I'm 42 yrs old and am the Founder & President of Sickle Cell Warriors of Texas. I have had several surgeries & blood transfusions from which I now have Iron Overload. I Advocate for Patient's Rights and Education on SCD.

Please discuss your SCD Story:

I was diagnosed at the age of 2 yrs old. SCD feels like a Charlie Horse on Steroids that doesn't ever loosen up. It's a Daily thing, from Swelling to Pain. I am unable to work and lately I have been experiencing Extreme Fatigue & sleeping a lot.

Please discuss any experience with chronic pain:

My Sickle Cell pain feels like a Cramp or Charlie Horse times 20 that won't stop. The longest I have experienced consecutively is 4 1/2 months, but some Warriors hurt Everyday. There are Several activities I can not do starting with Work. I have missed Several Holidays including my Birthday due to Sickle Cell Pain.

Please discuss any experience with management of sickle cell pain at home:

To manage my pain at home I alternate my prescription meds with tylenol or BC Powder and increase my water intake. I've had about 6 crises last year, and went to the ER maybe 3 times. I don't go to the hospital if I see that my meds are working at home.

Please discuss any experience with fatigue:

I am Often fatigued, it's a Daily Struggle. Sometimes I may sleep 12-16 hrs. It limits my quality of life by hindering the achievement of Goals I have set for my life. I can't get up & go tackle Today's Goal when I'm fatigued and don't get up & out until 4-5pm.

Please discuss any experience with other complications:

I may not be where I want to be Financially but I have God in My Life and He takes care of All of those Emotional, Financial, and Spiritual situations.

Please discuss the unmeasured costs of sickle cell disease:

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

I probably spent \$200 dealing with SCD last month. I can't work because of SCD.

Please discuss the impact of stigma and discrimination:

They mean a Lot to me considering the fact that I have experienced it All of my life dealing with SCD. I believe that the Misinformation of Sickle Cell being an African-American or Black Disease has led to the Discrimination of the Patients. Even the SC Patients that are not Black get discriminated against because of this Misinformation. Race has impacted treatments, research, and access to care Greatly!!! It's sad to say the Powers to be don't look at Sickle Cell Disease as an Urgent Need, All because of the Misinformation that SCD is a Black Disease & They don't Care about Us like that!

Please discuss the impact of hospitalizations:

I have actually already reduced my hospitalizations. I haven't been admitted in 2 yrs. When I am hospitalized, I'm in pain the entire time until the crisis is over. Yes I have been rehospitalized 30 days or Within 30 days after being discharged. I've been rehospitalized 3 days after being discharged before.

Please provide any comments about the current or new treatments for sickle cell:

I have tried 1 for Sickle Cell and 2 for Iron Overload. The treatment for SC Originally was effective, in the beginning. After having taken this medication for 15 plus years, I have experienced a few of the Side Effects of taking it for Several Years. Not Good! The treatments for Iron Overload both were Effective with the latter one being More Effective than the previous ones.

Sincerely,

Daryl Rosborough

Drazor48@gmail.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Lashawn H.

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Family member or Caregiver in the sickle cell disease community.

Briefly introduce yourself:

I am the mother of a daughter who had sickle disease at birth and passed the disease at age 15.

Please discuss your SCD Story:

My daughter was diagnosed at 6months in 1991. It affected her daily according to how the weather was, if it was extremely hot or cold, it affected her health.

Please discuss any experience with chronic pain:

My daughter's pain was horrific, she had it in her joints, upper thighs and lower back. Her pain crisis would last for 7-10 days every 3-4 months

Please discuss any experience with management of sickle cell pain at home:

Her pain was manageable at home 1 out of 4 crisis, she would have to go to the hospital the other 3, cause the medication at home couldn't manage the pain

Please discuss any experience with fatigue:

My daughter didn't suffer from fatigue it was all pain crisis

Please discuss any experience with other complications:

It's definitely taking a financial toll on our family, because you aren't able to work when your child is hospitalized.

Please discuss the unmeasured costs of sickle cell disease:

My daughter missed 30-50 days out of the school year and I missed maybe the same amount of days per year because of her disease, copayments for medicine was about \$700 per year.

Please discuss the impact of hospitalizations:

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

It would make a huge impact if my daughter didn't have to be in the hospital for a year. It's very stressful on families when loved ones are hospitalized you have to pay for food and parking while there with loved ones, time missed from your job.

Please provide any comments about the current or new treatments for sickle cell:
My daughter took hydroxyurea for about 5 months before she passed.

Sincerely,
Lashawn h
Terneylove@yahoo.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Zaynab Kareem

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

Am the first child of my parent and am a warrior battling with sickle cell disorder

Please discuss your SCD Story:

I was very young when I got to know I am battling with SCD. I never knew what it was until my first crisis. I thought I was going to die because the pain was too much but to my greatest surprise I felt better again after some weeks. Being a child I experience the pain in the leg very often but thank God my mother was always there to help.

Please discuss any experience with chronic pain:

My pain could last for a week and I won't be able to go to school, I would cry everyday that I want to go to school, my mum would satisfy me and get me dressed up buh at the end of the day, I won't be able to walk. There are sometimes I wont be able to eat just because the pain is in my hand,so my mum would have to feed me.

Please discuss any experience with management of sickle cell pain at home:

I would always try to manage my pain at home because I don't want my parents getting worried and I don't want my younger siblings to see me cry. I visit the hospital at least every four months.

Please discuss any experience with fatigue:

Even at this age I still get a lot of fatigue even as I am typing right now.my fatigue is almost everyday, I get tired easily.

Please discuss any experience with other complications:

Emotionally, I would cry even when I am not in pain because to me I give a lot of stress to my parents. When I was younger I used to consider myself as a burden to my parents even though they never complained to me.my parents would have a series of fights because of me. Financially, God has been faithful to us.we are middle class people and my father has always bought my drugs regularly and paid my hospital bills

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Please discuss the unmeasured costs of sickle cell disease:

A lot was really spent on me for my drugs, medical expenses, food, water etc. I could remember a time when I couldn't eat well but I had to use my drug, things were not going on fine with my dad then and he used his last naira to buy me multivitamin so that I could eat and use my drugs. My parents are the best. My mother wasn't working then but she would stay up all night watching over me and massaging my body whenever I had a crisis.

Please discuss the impact of stigma and discrimination:

The stigma was much especially when I was primary school, if I missed school for like two weeks and I was resuming back to school I would hear some of my teacher whispering to themselves about me being a sickle cell patient, while some of my classmate would bully me that I get sick everyday and am not as strong as they are.

Please discuss the impact of hospitalizations:

I already lost count about how much I have visited the hospital.

Please provide any comments about the current or new treatments for sickle cell:

I have been taking paludrine and sickle cell syrup and it has been of great help.

Sincerely,
Zaynab Kareem
Kharymzheeynarb@gmail.com

Crystal Rivas

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Family member or Caregiver in the sickle cell disease community.

Briefly introduce yourself:

My name is Crystal. I am 33 years old with 3 beautiful kids ages 13,11and 7. I am a mother who will not give up on letting the world know how much Sickle Cell affects my son and our entire family. We are from Hispanic descent and we did not know what was sickle cell disease until I got pregnant. I plan to keep educating our communities to help stop the cycle.

Please discuss your SCD Story:

When Joey was born he was diagnosed with Sickle Cell Anemia. He is now 7 years old in the second grade. Joey's first crisis was at 5months old and was hospitalized every 4 to 6months for spleen sequestration crisis, acute chest syndrome and asthma. Due to SCD complications Joey's spleen was removed at two years old. When Joey was 3years old he received his first blood transfusion. At the age of 4 he was diagnosed with asthma that lead to respiratory problems like acute chest syndrome. SCD affects Joey learning skills, such as thinking, reasoning, and remembering. When He misses several days in a row of school we are working hard to catch up with the rest of the class. We are wishing that one day he will be sickle cell free.

Please discuss any experience with chronic pain:

Joey describes his pain as " I feel like someone is punching me continuously". When Joey is in pain he is not able to participate in school activities such as gym or outdoor recess. When the pain becomes severe he does not attend school or is involved in any family functions.

Please discuss any experience with management of sickle cell pain at home:

Joey is in daily pain so we try our best to manage his pain at home with different home remedies such as hot packs, warm showers and massages . Joey is on hydroxyurea and was not admitted in the hospital last year but has suffered several pain crises at home and in school. We try to avoid hospital visits due to long stays.

Please discuss any experience with fatigue:

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Joey experiences fatigue leaving him extremely exhausted and dizzy. Waking up and going to school or attending events, family gatherings is really challenging for Joey. There's times Joey can not even walk to the park because he is too fatigued.

Please discuss any experience with other complications:

SCD affects the whole family emotionally and economically. As a caregiver and parent it is a constant worry about when is the next crisis or admission to the hospital. It has a huge impact on us financially not being able to afford meals during hospital stays or medical expenses like medication. I am not able to keep a job because of all the pick up calls I receive from school when Joey is in a pain crisis, feeling very fatigued and all the hospital stays.

Please discuss the unmeasured costs of sickle cell disease:

On average we spent close to 1,500 last month. One time we stood in the hospital for 10 days and I spent a total of 300\$ just being in the hospital.

Please discuss the impact of stigma and discrimination:

People often think sickle cells are a "black disease". Racism has affected the care for people living with sickle cell disease and health care equity issues.

Please provide any comments about the current or new treatments for sickle cell:

Joey takes hydroxyurea and has been taking it for 1 year now. It helped him make 1 year hospital free however he has been dealing with some of the side effects like nausea , brain fog,loss of hair, loss of appetite.

Sincerely,
Crystal Rivas
Crystalrivas973@outlook.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Erica Dunnam

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

My name is Erica I am 29 & I am a WARRIOR!!!!!!

Please discuss your SCD Story:

I was diagnosed at 14 months.

Sickle Cell to me feels like a great day gone bad when a crisis comes along. Feels like the worst pain imaginable it's really tough to put into words. I experience symptoms daily sometimes if my body does well 3-4 months. Sickle cell impacts my day to day life in many different ways some days are much better than others and some are horrible from the start.

Please discuss any experience with chronic pain:

My pain feels like being hit in multiple places all at the same time continuously. The length of my pain can last anywhere from 2 days to weeks. I am an active person and when these crises occur everything comes to a COMPLETE halt.

Please discuss any experience with management of sickle cell pain at home:

At home I manage my pain by first trying my home meds, then I try taking hot baths drinking something warm applying muscle rub on my hurting areas. I'm the last year I believe I've had more than 15. I've been hospitalized for about 7 of them. I don't go to the hospital until my pain is unbearable because of the treatment and the way the medical staff a lot of times treats & looks at me just because I have Sickle Cell. Which is a disease I did not ask for.

Please discuss any experience with fatigue:

My level can be highly times to where I feel like I have to push myself to do things. The frequency is at least 4xs out of the week. Fatigue limits my quality of life by stopping me from getting things done, starting projects I love, pushing my school start dates back, and even enjoying time with my loved ones.

Please discuss any experience with other complications:

Yes it's caused me emotional, much stress, passing on trips, & financial stress.

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Please discuss the unmeasured costs of sickle cell disease:

At least \$240.00

I have lost a lot that I wouldn't know where to begin. Yes I have too many stories. From calling the insurance company to doctor's visits.

Please discuss the impact of stigma and discrimination:

When I think about previous visits the discrimination and stigma comes in when the dr looks at me and says you don't look sick or your labs look fine to me. Race plays a major role when it comes to this disease as well as the treatment you receive.

Please discuss the impact of hospitalizations:

It would mean endless possibilities for me. It would be amazing. Honestly it used to be easy but now it's like hell. Going back and forth with what seems uneducated & uninteresting doctors & pain management doctors who think they know what works best for me is the most ridiculous thing I've ever had to do. Yes, I have had to be rehospitalized.

Please provide any comments about the current or new treatments for sickle cell:

I have tried 4-5 different treatments to manage & 2 of the 5 were effective. I've experienced upset stomach, increase in crisis, and a change in my hemoglobin.

Sincerely,
Erica Dunnam
ericadunnam_7@yahoo.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Whitney Smith

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

I am 34 years old looking and wanting to be in the entertainment industry and very passionate about it too. I want to do acting and voice over. I received my Bachelors Degree in Theatre Studies from UNLV in 2010. I did after graduation did an internship in Pahrump, NV at their local television station doing interviews as well as letting me do an entertainment segment. While there I did do some background extra work for various projects. Since then I moved to Los Angeles to pursue my career further. While living here I as well done background extra work, but nothing major as of yet. Love mermaids, Mickey Mouse. When I have time I like to go bike riding, play games, board games as well as video games, go out to eat but what I especially love to do is go to the amusement parks. I consider the amusement parks the club for me. I am a BIG roller coaster junkie. In addition I occasionally like to write short stories putting my characters in peril situations.

Please discuss your SCD Story:

I was diagnosed with Sickle Cell Disease when I was about two weeks old. SCD is like an annoying little sibling (I think of her as a sister) that won't go away and we are constantly fighting and she is hitting me more than I am and her hits are causing me more pain. SCD impacts my life in more ways than people can understand. The word "normal" does not exist in my life. I have to find different, creative ways to deal with SCD as well as just trying to live. Sometimes the pain is so unbearable you don't want to even go to the bathroom.

Please discuss any experience with chronic pain:

The ways I can describe how SCD pain feels like is a throbbing, stabbing, sharp, aching, like someone has tied a rubber band around the area that's hurting or like someone has steel toe boots on and just repeatedly kicking me over and over. The pain is so bad sometimes I feel like I want to rip my skin off and scream. Crisis usually lasts for 2-3 weeks but for me it's been hard to say how long a crisis lasts because I have been in an ongoing crisis for months and months. If I have gotten one area control another area in my body starts up. I call it "new pain" because it is more sharp than the pain you have kinda tamed. Seems like the pain is worse at night than in the day. When this happens you are quickly rushing to take it and get some kind of relief. For me taking

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

my pain meds, massaging it, getting in a tub of water. When my mom hears me do this she knows what's up. What's really worse is when a crisis wakes you up out of your sleep at 2:00am-3:00am. It is pure torture and it seems like it takes forever to get any relief, but when you do you want to very still because any slight of movement would seem to aggravate it and usually by the time you have some relief the sun is coming up because of the battle you have been fighting during the night which now I am trying to make the executive decision to call of work or not go to school. Because I have been in this ongoing crisis it has limited me from doing or being involved in activities. I think SCD has ears or something because anytime I want to do something fun SCD pops up which the majority of the time I have rescheduled or cancel. It has definitely affected me going to work.

Please discuss any experience with management of sickle cell pain at home:

I manage my pain at home with pain medication, heating pads, hot water bag, tub of warm- usually-hot water with epsom salt or scented epsom salt, pain relief ointment like Icy Hot, Bengay, plug in massager. In the hospital my pain is managed with IV pain meds, round the clock IV fluids, heating pad, hot packs. As said before it's hard to say how many crises I have had in the last year because they have been ongoing. Seems like once I get one area controlled another area starts up. I have decided not to go to the hospital because most of the time it's not my decision. It's someone else's decision (like my mom's) and we get into it because of that reason. So to avoid confrontation I chose not to go even though that's not good for me because I'm the one that is suffering. Also deciding not to go to the hospital because being stereotyped. I call SCD the "black sheep of diseases" because it doesn't get the respect it really needs and deserves. Another reason I hate coming to the hospital is when sickle cell patients are admitted especially on the Hematology/oncology floor if they always sickle cellers float nurses. Personally, I HATE float nurses because the majority of them have not dealt with sickle cell patients, they don't know how crucial it is to be on time and STAY on time with the pain meds. Basically you can't tell them anything because they think you are trying to do their job. And that leads me back to sickle cell being the "black sheep" of diseases and cancer being the "privilege" disease. When they have a lot of oncology patients they HAVE to give the seasoned or the OG nurses them where sickle cell patients get the bottom of the barrel or floats again showing that sickle cell care is not as important as cancer or any other disease. It's not fair, just not fair!

Please discuss any experience with fatigue:

I feel like my level of fatigue is high. I am tired most of the time. Not only does pain hurt but it wears you out. So I am tired most of the time. I want to go out and do fun things but be too tired to do it. I feel I spend most of my time in bed rather than trying to enjoy life.

Please discuss any experience with other complications:

Aside from the pain crisis SCD affects my relationship with my loved ones emotionally. My mom tends to say a lot of hurtful things in regards to my SCD and no matter how you put it words hurt and once you've said them you can't take it back. She makes it seem like it's my fault I have SCD and I'm the one that causes it where I didn't ask to be born. She says she hates to see me in the pain I'm in because she feels so helpless, and I used to believe her but she does it every time I'm in the hospital or in pain. But to me she has the tendency to forget even though she's going through it emotionally, I am going through it emotionally AND physically. So in order not to put the blame on herself and make it seem like it's her fault I'm the sacrificed lamb.

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

And in order to try to avoid confrontation I just say things she likes to hear because her mouth is worse than the pain I'm going through and that causes stress and she out of all people know that stress is the trigger of a crisis. SCD does have an impact on my life financially because when I'm in crisis or in the hospital of course it causes me to miss work and life doesn't stop especially when you are in the hospital.

Please discuss the unmeasured costs of sickle cell disease:

I don't know how much I spent on sickle cell in the last month or so. To me it feels like a million dollars. From going to treatment to hospital stays. One story on a hospital stay is Medicare wanted some paperwork which was really unnecessary, felt like dipping and dapping and being nosy but I was in the hospital and they needed some paperwork back, so my mom used a lot of gas by bringing the paperwork up here to the hospital for me to sign it then had to take it back to the place which was pretty much on the other side of town along with the traffic she had to deal with and yet along I had to hear all this too even though she was helping me.

Please discuss the impact of stigma and discrimination:

As I have said before I call sickle cell the "black sheep of diseases" because to me I feel race is involved and because it mostly in the African American community a lot of medical personnel don't want to deal with it and give it the attention it really needs and deserves when it comes to treatments, research, and level of care. You don't see any commercials about SCD, or billboards or bus stop benches. So people that have sickle cell advocate it to make their voices heard about it. Sickle Cell patients are very much judged and stereotyped. When you say cancer, diabetes, lupus, people know exactly what it is and what it does, but mention SCD most of the time you even look confused. It's either "I've heard of it but don't know what it is" or "what is that?" Even mental illness & autism gets more attention than SCD. SCD is an invisible chronic illness but people don't know how serious it is. It's serious like any other disease. SCD gets very much judged or stereotyped. We have been called "attention seekers", "druggers", "drug addicts", "fakers". We also don't like to go to the hospital because of these reasons and more. When we go to the ER it's like waiting for an eternity. They will take people that have a stomach ache or paper cut or a cold over a sickle celler. Then medical personnel think we are faking when we tell them we are in a pain level of 10 but we are on our phone. Yes we are on our phone to distract ourselves. Because if we scream we are causing a disturbance to the hospital. Then we have to fight for our pain meds and make sure the nurses are on time. And some nurses don't seem to care about being on time. Their excuse is "I was in a room with another patient." I understand you are busy with another patient and of course I wouldn't want you to take your attention off your current but you are not the only nurse on the floor. If you feel you can't get away call another nurse to give me my pain meds. It's not fair or right I get off schedule because you were busy with another patient and when you are late since my meds are a narcotic the later the nurse comes the later I get off schedule and it's CRUCIAL to stay on schedule as much as possible. Then it's like we have to prove we are the amount of pain we in to get a higher dose of pain medicine where as a cancer patient could ask for a 100 mg of pain meds and no questions ask, if a sickle celler does it we get interrogated. What's really the killer, doctors seem to send us home early when we know we aren't ready. And usually when they do that we end up coming back within a 12-24hrs period and sometimes it's something worse than just a crisis. Doctors need to realize it's not just about pain and pain meds.

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Please discuss the impact of hospitalizations:

When you have to call the hospital your second home majority of your life says a lot. When you are in and out of the hospital like that can cause an emotional strain on you and your loved ones. Emotions are very high. Have I ever been rehospitalized 30 days after being discharged? I have been re-admitted 12 hours of being discharged which all goes back to discharge too early or not being ready to go home. Now I'm back to go through all this torture again or being poked and prodded on, have multiple tests done, etc.

Please provide any comments about the current or new treatments for sickle cell:

I have tried multiple new treatments to manage my SCD and most have been ineffective. Some stated they would reduce the amount of pain crisis, false. I feel I have the same amount of pain crisis if not more. Some have stated to reduce the amount of hospitalizations, again false. Majority of the new treatments that have come out don't do what it states it's supposed to do. My friends that also have SCD have said the same thing, so I know it's just not me experiencing these symptoms and side effects.

Sincerely,
Whitney Smith
mickey200103@yahoo.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Marchell Newton

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

I have SS

Please discuss your SCD Story:

My Momma told me that I was diagnosed at 8months, living with SCD can be very PAINFUL at times, there's times when I experience pain at least every other week in the winter, living with SCD is very difficult in my life, being the main supporter of the family it's times that I go to work in some form of pain, and the only medication I can take is IBP, that only helps so much.

Please discuss any experience with chronic pain:

My pain at the highest level feels like arthritis x20, the pain can last at the x20 level 10 days, but at a low level 1-6 anywhere from 2 to 5 days. Activities are very difficult to do, sometimes I have to go to work or play with my grandkids.

Please discuss any experience with management of sickle cell pain at home:

I manage my crisis with T3's (Tylenol 3 with Codeine) and or IBP, when that doesn't help it's the hospital. The last year I had probably 5 very painful crisis with the 5th one landing me in the hospital for 10 days. The reason that I didn't go to the hospital for them other 4 painful crisis is that I didn't feel like waiting in a long line, being judged as a drug addict, I rather stay at home and suffer there.

Please discuss any experience with fatigue:

With fatigue I have to rest more, kids really don't understand that so I have to push myself knowing that there's a possibility that crisis will occur, fatigue is part of my life.

Please discuss any experience with other complications:

Having SCD can have an affect on one's mindset, like suicide or wanting God to take your life because the pain can be unbearable, but with me I say what the hell I have a family to enjoy and if I take my own life my family will feel a more different pain. Financially I do okay, but medication takes some of that money too.

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Please discuss the unmeasured costs of sickle cell disease:

Only thing I can say about this is IT COSTS!!

Please discuss the impact of stigma and discrimination:

Being Black and drugs are evolved, and the history of the Negro!! Treatment has gotten a little better but a long way to go.

Please discuss the impact of hospitalizations:

Yes I have been through this more than once.

Please provide any comments about the current or new treatments for sickle cell:

Hydroxyurea, Endari, blood transfusions, ill take blood transfusions anytime but the iron overload is dangerous, blood transfusions gives me a chance to have a active lifestyle without worrying about any crises that might be waiting for me 😊, Hydroxyurea and Endari helps me control the pain better.

Sincerely,
Marchell Newton
lilnewt6@gmail.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Marissa Cors

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

I am a 5th generation Sickle Cell patient, advocate and care giver. As well as, community educator and outreach coordinator for my families non-profit Axis Advocacy for Sickle Cell.

Please discuss your SCD Story:

I was diagnosed at months old via letter. Being that I am a 5th generation carrier my family had a long standing relationship with SCD. Therefore, they were somewhat prepared for what was to come. Living with SCD is to have a life with an illness that you didn't ask for, want or need. Yet are constantly, faulted for its drawbacks, medical professionals education and care practices and the stigmas and stereotypes mostly, as being a drug seeker...but, still must take responsibility for what it brings. The responsibility of taking daily medication, watching your water intake, how much energy you use and for what, how to manage the decision makers in your life i.e. teachers, parents, doctors, and the general public's outlook on what being sick should look like.

Please discuss any experience with chronic pain:

It feels like a hard throbbing, stabbing motion in my right knee and left clavicle where the cartilage has been worn down and damaged over the years. It can last anywhere from a few minutes to days. Sometimes it can be managed at home and sometimes you need more help and have to go to the Er or the hospital. This forces you to negotiate your activities like going to school, work or social outings. Basically, trying to maintain your responsibilities in the midst of severe pain. Then, calculating whether or not you will be able to do those things in the days to come and for how long? Often you are seen as being lazy, irresponsible, and unreliable to co-workers, bosses, student groups etc. regardless of the fact that you are acting as responsible as you can in the given situation.

Please discuss any experience with management of sickle cell pain at home:

I take my home meds as prescribed over a course of 3 days if the pain should persist that long. If after the 3 days the pain isn't getting better or even worse then, I go to my md. After which its decided if I will go to the outpatient infusion center or the hospital.

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Please discuss any experience with fatigue:

Fatigue is the worse of the symptoms because its not something that you can readily describe, prevent, or get rid of quickly../there's no cure other than rest. How much rest does it take? That's the question that's very hard to answer because you cant quantify the cure. Unlike, with pain in which, you can take actual pain meds...multiple pain meds and have an actual number of hours in which you can use to navigate the crisis and where its going. Is it getting better, worse, or staying the same? Usually, there's a plan put in place to help you through the pain but not the fatigue.

Please discuss any experience with other complications:

Due to the pain and chronic fatigue, all aspects of your life are affected and you are responsible for the outcome regardless of it being your fault or not.

Please discuss the unmeasured costs of sickle cell disease:

Due to sickle cell I rejected a blood transfusion at 19yrs old. As a result, of that I passed out on campus and lost 4days of my life. When I woke up I was ina private room with no recollection of how I got there or what happened. I was soon told that I'd rejected the transfusion and my parents had spent almost a week trying to get me transferred to my home hospital. However, the hospital I was in didn't want to release me because they were concerned about their liability. As a result, I accumulated multiple antibodies, had a hemoglobin of 1 and went into systematic organ failure in a separate crisis 3 yrs later. I can no longer receive blood product of any kind that means no children, major accidents, cutting myself with a kitchen knife etc...But most importantly, it means that when I go into crisis and have to be hospitalized I cant be transfused....ever. Since mds don't read charts anymore, their first instinct is to dO just that. This means I have to be on top of everyone charged with my care to make sure they don't kill me. This also means that my stays are extended by weeks just waiting for my body to recover naturally. By naturally, I mean being hydrated 24/7, being given iV pain meds around the clock and antibiotics to treat infections I may come into contact with while in the hospital.

All together I have spent about a third of my life in hospitals, infusion centers, md offices etc. It has cost me jobs, opportunities and income.

Please discuss the impact of stigma and discrimination:

We are often labeled as drug seekers because we often are sent to the Er for pain management. This makes no sense because the medical professionals know that SCD causes immense pain. Pain unlike anything and yet they are constantly, questioning if our crisis is real and how bad is it really? Why is it ok to ask that? Why is it ok to question if we are really sick? They don't question cancer patients or aids patients these questions. Then, once we are labeled drug seekers and told that we are addicted. They then refuse to treat us as drug addicts which has a protocol but, not when it comes to sickle cell patients. This makes it hard to get the pain under control. It makes it hard to get proper care even from the nurses charged with your care because you don't fit their vision of pain. It sucks.

Please discuss the impact of hospitalizations:

Yes I have been hospitalized multiple times in a month due to doctors and administrators saying that I wasn't sick enough to be there. The cost of being hospitalized is upwards of 250,000 dollars a year in bills.

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Please provide any comments about the current or new treatments for sickle cell:

Ive been on Hydroxyurea for 20yrs. In the last 2yrs Ive started taking Endari which has helped me greatly reclaim my life. This month I will try the new drug Oxbryta. Since being on the Endari I have only been hospitalized for 2wks in the last 18 months. As opposed to 4-6 months a year between the years 2012 and 2017. I also, have incorporated medical marijuana into my pain regime and it has greatly decreased my use of opioids.

Sincerely,
Marissa Cors
corsmarissa@gmail.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Capricia Smith

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

Hello my name is Capricia im 28 and have sickle cell beta thalassemia.

Please discuss your SCD Story:

Ive always dealt with sickle cell but was officially diagnosed with the disease in 4th grade. SCD is a pain that can not be described, the pain is unbearable. Ive managed to get my main crisis down to twice a year but everyday i'm usually in some type of pain. I'm so tired and can't do much in one day.

Please discuss any experience with chronic pain:

When asked the question how SCD feels I'm never able to answer, the pain is something that can not be described. Working has been something I have been able to do for years, anything can cause a sickle cell crisis so you can't be to happy, sad, mad anything.

Please discuss any experience with management of sickle cell pain at home:

Overall when in a pain crisis I try to relax as much as possible and not stress the issue at hand. I am drained and do not like going to the er where the doctors just judge you.

Please discuss any experience with fatigue:

I'm usually very tired.

Please discuss any experience with other complications:

Im unable to successfully work which is draining.

Please discuss the unmeasured costs of sickle cell disease:

You lose alot of time.

Please discuss the impact of stigma and discrimination:

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Because it's known that more AA. Have sickle cells seems to lack knowledge.

Sincerely,
Capricia Smith
Capricia357.cs@gmail.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Destiny Beltre

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

Hello! My name is Destiny and I've been diagnosed with sickle cell since inside the womb. I had my first crisis at about 6 months. But I am not just my disease, I have many other things I love to do. I'm a 20 year old who, when I'm not sick, loves adventures! When I'm not at Disney world (my happy place) I'm hanging out with friends or trying to volunteer to do things around my community. Unfortunately I have much more chronic pain then most so I am often either in the ER, admitted or in some sort of clinic.

Please discuss your SCD Story:

I was diagnosed in the womb and had my first crisis at 6 months. SCD feels like being left out, being disappointed and feeling like you could be doing so much more even though your body won't let you. I experience pain EVERYDAY of my life. In the past month I have been in the sickle cell clinic three times a week every week (so 9 out of 21 days of this month) and the ER maybe 2 to 3 times as well (so all together about 18 out of 21 days of this month I have been out of work/school/activities due to being in a hospital or some sort of sickle cell treatment.)

Recently unfortunately that has been the reality of my life. Since I was about 16 I have been having incredibly chronic pain that does not ever give me a chance to catch my breath. It feels like the longest I can go before another crisis is a week. It's gotten to the point where I did not graduate with my class because I was out of school so often. And the school board of Broward County did nothing to try to help the situation I was in. I was responsible for getting all my own makeup work and when asking teachers for work ahead of time I was told no.

Please discuss any experience with chronic pain:

It feels like your bones are trying to cave in on themselves. It feels like someone is grabbing hold of my bones (mostly my ribs or joints) and holding onto them for dear life, as tight as they can and also pulling them as if hanging from them. It's so Debilitating that even the smallest of crises can make you feel like you're dying depending on the spot and severe ones make you believe that you'd rather be dead. This disease has kept me from things all my life. I didn't graduate with my class therefore I couldn't go to prom after getting promised I would be able to attend. I wasn't able to play with the other kids growing up because I would play myself into episodes. The

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

moment I started playing sports I had to get my hip replaced and was told I was no longer allowed to run. How do you tell a 14 year old they are no longer allowed to run? The amount of times I had to cancel on friends or family plans because I was in the hospital is phenomenal. I actually had to leave the hospital against medical advice because on my 20th birthday I was supposed to go to a special SOLD OUT Disney event for Halloween (my favorite place and my favorite holiday all celebrated on my birthday) and I refused to miss it. It was one of the worst episodes I had in a long time and I refused to miss something as important as that after consistently missing events the entire month.

Please discuss any experience with management of sickle cell pain at home:

Sometimes going to a hospital and having to fight to be taken seriously is more work than trying to stay home and fix it alone. I put my health in serious risk often because I would rather stay in my home than go to a Hospital and be treated like a drug addict or like I'm faking. I often refuse being admitted because my hospital that I've gone to since I was seven has a brand new pain management doctor that refuses to, get this, manage pain for sicklers. She would rather you be in pain with fluids and oxygen then try to help and won't even talk to you herself but through other people.

Please discuss any experience with fatigue:

I am often fatigued. I can't do normal things like the beach or parks with friends and family because of it. I often stay home while friends go out and do things because I know if I go out with them I will end up passing out, being left out, or having to go to the hospital the next day.

Please discuss any experience with other complications:

Emotionally this disease is so taxing. I had horrible mental health for a long time because of it. Not to mention the strain in relationships after being in and out of hospitals for months.

Please discuss the unmeasured costs of sickle cell disease:

I luckily am under Medicaid for children and they are the only reason I am not in an immense amount of debt. The amount of times I'm in hospitals and doctors offices and the resources I use for my disease I would be billions of dollars in debt without the government's insurance. I also cannot work due to this disease. Also my significant other who is my main caregiver has missed work many times due to emergent hospital trips or having to stay up all night in a hospital with me.

Please discuss the impact of stigma and discrimination:

If this disease didn't affect just brown and black skinned people it would've been cured already. Because this disease only affects dark skinned people it's not taken seriously and not as a priority. The amount of times I have stereotypes as a woman looking for pain meds bc of my darker skin is disgusting. The fact of the matter is I hate pain meds, I hate how they make me feel, look and act and if I could go another day in my life without them I would do it in a heartbeat. But because I come in as a young brown woman I almost always immediately type casted as drug seeking. The pain management at the hospital I'm always admitted to has made that very clear as well.

Please discuss the impact of hospitalizations:

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Even being hospitalized one less time a year would be amazing. That's one less time I'm without friends and family. One less time in pain and depressed. One less time I'm being shamed for needing pain medicine or being type casted as something I'm not. Being in the hospital is the most defeating things that can happen to you. The moment you're admitted you know you'll be there for at least three days. Alone in a room you can't leave in a bed you'll only get up from to pee. With minimal contact with the people you love.

Please provide any comments about the current or new treatments for sickle cell:

The last time I had a new treatment for sickle cell was the start of middle school with hydroxyurea. It was an amazing treatment and helped intensely with my anemia. I am supposed to be in a clinical group for a new medicine soone to hit the market for sicklers that is an infusion base and hopefully I won't get the placebo.

Sincerely,
Destiny Beltre
destinyart03@gmail.com

Terrance Hill

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

My name is Terrance, a 40-year-old determined individual who was born with Sickle Cell Disease (SS) and although I don't look like what I have been through, although I have been through a lot. The complications which I have faced when they have arisen not only defines the word warrior but my character I display with each encounter.

Please discuss your SCD Story:

When I enlighten the world of my parents I was born with a gift name Sickle Cell which was meant to hold me back but as a true warrior my motto better yet our motto for any other person who lives with the challenges of Sickle Cell is "I have Sickle Cell but Sickle Does Not Have Me". As a child the toughest obstacle that I faced was suffering a stroke at the age of 7 and to not only having to rebuild my strength physically to get around but mentally as well. When transitioning from a boy to a young man who becomes a man, the hardships I endure as I look back at it now made me empathic as it took away moments with family and friends due to chronic pain complications or medical procedures I had to be hospitalized for.

Please discuss any experience with chronic pain:

The pain that I experienced was excruciating especially during the winter months. Keep in mind that having to stay bundled up to stay warm is good practice, but unexpected crises can happen at any given time. My pain usually lasted for a few days by treating myself at home with prescribed medications and when the pain could not be subsided a trip to the hospital was needed for the best form of treatment was to relax while I recoup.

Please discuss any experience with management of sickle cell pain at home:

In order to manage my pain at home some of the techniques that the medical staff at UIHealth implemented was keeping track of my blood counts and making sure that medications were filled so I have treatable methods to prevent hospital admittance.

Please discuss any experience with fatigue:

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

The level of fatigue can also trigger an attack and to prevent this occurrence staying replenish with fluids is mandatory.

Please discuss any experience with other complications:

The other complications of SCD that impacted my life were needed surgeries such as my total left hip replacement. Living with pain is what defines me at times but when that pain becomes unbearable for me to walk without losing my balance, I knew a solution was needed asap.

Please discuss the unmeasured costs of sickle cell disease:

The unmeasured cost of Sickle Cell is ridiculous. When I was finally scheduled to have my total left hip replacement surgery the week before I'm preparing myself to have my surgery I received a call from Rush hospital stating my insurance had been cancelled and in order to reschedule I would have to get reinstated. This occurred during the Christmas holiday which the only gift that I wanted that year was to have this surgery. In order to get my health insurance, I had to visit the aid office in the worst pain I ever been in just for them to witness the agony I was in before reinstating my health benefits.

Please discuss the impact of stigma and discrimination:

The stigmas and discrimination of Sickle Cell Disease is unbelievable because we are living with conditions that are intolerable and the need for medications is not all that we are looking for. On the other hand, Sickle Cell does not only affect Afro-Americans but other ethnic groups as well.

Please discuss the impact of hospitalizations:

Whenever I'm hospitalized, I miss my family and being able to reduce the time I'm in is mandatory because I feel like my sleeping patterns are completely thrown off. I have been hospitalized 30 days after being discharged due to acute chest syndrome that calls for another stay in the hospital.

Please provide any comments about the current or new treatments for sickle cell:

As a young adult my medical staff informed me of a clinical trial for hydroxyurea which I didn't hesitate to volunteer but unfortunately, I was not able to stay in this study since it was not beneficial for me. Many years later, I found myself having a Stem Cell transplant to cure the complications I endure living with Sickle Cell Disease.

Sincerely,
Terrance Hill
Terranceh31@gmail.com

Deonar "Mz.Dee" Gilbert

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

My name is DEONAR GILBERT. But everyone calls me MZ.DEE. I am 39 years young. I am a mother of 5; 1 daughter 19yrs and 4 sons ages 14, 12, 10, and 1. I was a Paramedic/EMT in Atlanta, Ga for 12 years. I am also a survivor of domestic violence. I consider myself a true Warrior/ Overcomer in more than just one aspect of life.

Please discuss your SCD Story:

I was diagnosed with Sickle Cell in 1981 when I was born. Sickle Cell has always been a part of me. I remember in grade school missing 14 days out of school at times due to Pneumonia and shortness of breath. Always around my birthday time in the middle of winter. It would be difficult to walk around my home cause I would get short of breath going from my room just to the bathroom up the hallway. Sickle Cell has become so much more painful for me now that I am older. The pain crisis is unbearable at times. My pregnancies were tough, not easy nor smooth. Now that I'm a mother, a caregiver, student, and becoming an entrepreneur, I wear many titles. The most important one to me is Mother. I love my children with everything in me. They all have a Sickle Cell trait but not the disease. I'm grateful for that. They see more than anyone else around me what it's like to live with Sickle Cell. The ups, the downs, and the lows. They see how I'm more bedridden nowadays due to uncontrollable pain. I just can't get up at times to clean or to cook or to even just play a game of Monopoly/Family Friday Time. I do the best that I can do to work with my current medical team to get my pain under control so that I can at least appear normal or partake in normal daily activities. I experience pain everyday. And that's not easy to deal with. Every morning I have medication that I take to get my day started. Some mornings are better than others. About 2-3 times out if the week I have to take around the clock meds to be able to get up, bathe, clean my home, spend time with the kiddos, go outside, etc...

Please discuss any experience with chronic pain:

The pain I experience with Sickle Cell sometimes can not be described. It can be sharp, achey, stabbing, cramping, soreness, tenderness in legs, arms, stomach, back, or hands and feet, if touched. Sometimes the pain can start in one area and radiate to other areas of your body or trigger other areas of the body to begin to hurt. The pain can last anywhere from 2-3 hours up to

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

3-4 days or weeks at a time. I have realized now that I am older I have more frequent pain crisis than in my younger years. The intensity of the pain has also increased. I love going to church and singing on the praise team and/or dancing with the dance ministry. I have not been able to participate in those activities in about 2 months. I haven't been to church in about 5 weeks now. I'm grateful to be able to watch the service through social media, but it's just not the same as being there physically.

Please discuss any experience with management of sickle cell pain at home:

I manage my pain at home with oral medications. I take Lyrica, Percocet, Ibuprofen, Promethazine, and I wear a Fentanyl Patch. I have to take these medications everyday. All days are not good days. Some days the medication just doesn't control my pain. The pain never completely stops. You just have to adjust to it and do what you can do to continue to move forward in life. I don't go to hospitals unless I have exhausted all meds and resources at home and the pain won't subside. I'm a single mom and have no help when it comes to caring for my kids while I'm in a hospital (except my 19yr daughter who works).

Please discuss any experience with fatigue:

I have little energy to keep up with my sons including my 1yr old (who has a plethora of energy). It's hard to tell them I can't come outside to watch them ride their bikes. Or ask them to eat cereal for breakfast cause I just don't have the energy to stand and cook. I have to push myself daily due to them being homeschooled. I have even had to hire someone to do P.E. and Art with them because Sickle Cell doesn't allow me to do these with them everyday. I am unable to do the things I once used to do.

Please discuss any experience with other complications:

I'm unable to work right now which takes a toll on my family finances and me being able to provide for them. I cannot stand or walk for long periods of time. I'm unable to sit at a desk for long periods of time. Between the pain and low energy, I am barely able to take care of my family yet alone hold down a job. I have applied to school but only online classes I can do at home at my own pace. Emotionally, I feel like I'm drowning at times. I feel anxiety and stressed out. I sometimes feel like why did I deserve this. What did I do wrong? Why do my children have to suffer for my illness?

Please discuss the unmeasured costs of sickle cell disease:

On a monthly basis I spend roughly about \$200.00 on Sickle Cell related items. From my meds that insurance won't cover completely to vitamins to fruits and water to stay as well and as healthy as possible. I remember the last week in May of 2019 I was hospitalized for 15 days. I had to send my children to a friend's house in another state to care for them while I was in the hospital. That hurt me just to see that I really had no one to support me or help me with family while I was down. My father died in 2006 and my mother passed away in 2007 since then it's just been my kids and I.

Please discuss the impact of stigma and discrimination:

I believe race has played a part in how Sickle Cell patients are affected and treated. I also believe race has played a part in research development, in treatment development, and accessing the

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

proper care and quality of that care. A lot of healthcare professionals have a stigma attached to Sickle Cell patients. They don't want to deal with us or they believe we are not in as much pain as we say that we are. They don't want to prescribe meds that they know will help subside pain. I feel as if sometimes they are wanting us to remain in pain. As if it's our fault we were born with this disease. We didn't ask for this. I wish there was more empathy, understanding, support, and knowledge amongst the healthcare field in its entirety for the Sickle Cell community. Why can't Sickle Cell be a priority like breast cancer awareness is? Or like diabetes awareness is?? I believe Sickle Cell doesn't get prioritized due to the people it affects. The Minority groups. The group of people that some in the healthcare industry don't care about or see as important.

Please discuss the impact of hospitalizations:

Having to go to the hospital takes a toll on my family. It upsets my children and disturbs the entire flow of my home. I've had to discharge myself early to tend to my family issues. I try my best to take care of me so that I can in return care for my children. That's sometimes not an easy task to accomplish.

Please provide any comments about the current or new treatments for sickle cell:

I have tried different oral medications. I am allergic to morphine and unable to take it. So I've had to try different meds to see what works and what doesn't. I am currently still on the road to finding what really works for me and what doesn't and so, my story continues.....

Sincerely,
DEONAR MZDEE GILBERT
mzdee2414@gmail.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Adeniyi Adejobi

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

43 by June 2020. Sickle cell since like ever (lol). Love writing. Make up stories in my head most of the time. I love to keep to myself.

Please discuss your SCD Story:

Since I was little, a baby. SCD is my life and also the thorn in my flesh. Complications, almost always, even due to my easy allergy reaction, I don't eat well, etc. Impact... Really don't know how to put it nicely, so SCD controls everything and every part of my life.

Please discuss any experience with chronic pain:

Hhhhhmmmm... Pain is part of how I know I am still alive. Like a quote I read once before... If I wake up tomorrow, and I don't feel any pains, my next question to whoever I see 1st is: "How did I die?"

Please discuss any experience with management of sickle cell pain at home:

Like I said, pain is my life. I don't like going in to hospital for pains, but if I can't bare it no more, I'll go in to get stronger and faster meds. That's all.

Please discuss any experience with fatigue:

Fatigue comes and goes. Like my pains, I have adapted to it... That not many knows I have it.

Please discuss any experience with other complications:

Yes, emotional, money, always thinking, preferring to be by myself always, etc. I just accept it as part of being SCD.

Please discuss the unmeasured costs of sickle cell disease:

I hate my family missing out because of me. So I usually let myself do the missing thing. Cost... Seriously, I can't value it. However, if I don't have SCD, I'll be a millionaire in my twenties!

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
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Please discuss the impact of stigma and discrimination:

I don't know much about the race thing... Because, I grew up in Africa and we are still discriminated against like we were born to die young or die when we most needed. So I don't think it's about race... Just my thoughts.

Please discuss the impact of hospitalizations:

I hate hospitals. I won't lie. I despise it. No matter how good I am treated. It's still my worst days, so I try to avoid hospital stays. Simple.

Please provide any comments about the current or new treatments for sickle cell:

I'm sorry. I lost count. Some work, some made it worse especially due to my body reacting fast to things it doesn't like... So I am sorry, I can't give much details to this question.

Sincerely,
Adeniyi Adejobi
seun313@yahoo.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Cierra E.

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Family member or Caregiver in the sickle cell disease community.

Briefly introduce yourself:

Hello, I am a mother of 3, two boys and a girl. My daughter is the youngest, 3 years old and has Sickle Cell SS.

Please discuss your SCD Story:

My daughter was diagnosed with sickle cell when she was 7 days old. When she was 18 days old, we started our journey of being in and out of the hospital. She had frequent fevers and dactylitis. I had to resign from my job to care for her while she was in and out of the hospital. I am currently back to work and have missed 25 days since October 2019 because my daughter has been in the hospital with fevers, pain crisis and infections.

Please discuss any experience with chronic pain:

My daughter's pain is so excruciating that she can't walk and sometimes I can barely hold her because every movement causes her to cry out from the pain she is in. A lot of times ibuprofen, Tylenol and heating doesn't help so, we have to go to the hospital for stronger pain medicine such as morphine, etc. Her pain lasted 2-7 days which caused her to miss many days of preschool, which caused me to miss many days of work because I have to stay home and care for her.

Please discuss any experience with management of sickle cell pain at home:

I manage my daughter's pain at home with ibuprofen, Tylenol and a heating pad. Most of the time her pain can't be managed at home, so we have to go to the hospital. She had 4 or 5 crises last year. I took her to the hospital every time. I am scared of what the pain will do to her little body if I don't take her.

Please discuss any experience with fatigue:

My little girl stays so fatigued, she takes 2-3 naps and expresses how tired she is daily! We have to miss so much, whether it's a birthday party, family gathering or even my oldest sons sporting events because my daughter stays fatigued.

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
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Please discuss any experience with other complications:

Our lives have been impacted tremendously since my daughter has been diagnosed with sickle cell. We struggle financially because a lot of time I have to take off work to care for my daughter, which leaves my husband to have to work overtime to make ends meet for our family. We have medical insurance through my husband's job but the medical bills are beginning to add up. Emotionally, we are all drained, my older kids having to see their little sister go through the pain she goes through, myself because I worry nonstop about her health and also, because I have to miss out on so much my other kids are doing, sports, school events, etc. My focus and attention goes to my daughter because sickle cell consumes our lives. I spend a lot of days/nights crying and praying, wishing my baby could live a normal life, play without getting tired and live without pain.

Please discuss the unmeasured costs of sickle cell disease:

We spend on average 1,000 monthly to help keep my daughters sickle cell managed. When it's a month that she is running fevers or having a pain crisis and we are back and forth in the hospital we are spending \$1,200-1,300 for gas because the children's hospital in a city 45-50 minutes away, food, parking, and my daily needs while being in the hospital with her. I have missed work to take a whole day to try and get things sorted out with the cost of her hydroxyurea and refills of penicillin. Making payment arrangements on hospital visits, copays for hematology and pediatrics appointments. Money goes into Making sure she has thermometers, heating pads, ibuprofen, water, healthy snacks, elderberry syrup and vitamins just to name a few things. We struggle financially to make sure our baby has what she needs.

Please discuss the impact of stigma and discrimination:

I feel race plays a huge part in the reason why research, medications and care is limited. I have been asked so many times "isn't sickle cell a black people disease." I also feel that sickle cell patients are discriminated against and thought of as "drug seekers." The lack of knowledge and awareness about sickle cell disease is sad. I wish they would raise just as much awareness and research just as much as they do cancer, hemophilia and, HIV.

Please discuss the impact of hospitalizations:

It would mean everything to me for my daughter to have reduced hospitalizations and to be able to live "normal". Staying in the hospital has caused her to have nightmares because she is constantly being stuck because her veins blow. Seeing everything she goes through hurts me deeply. I would endure all of her pain if I could. The hospital stays are mentally, physically and emotionally draining. She has been rehospitalized a couple of times back to back.

Please provide any comments about the current or new treatments for sickle cell:

The only medications my child takes right now are Hydroxyurea and penicillin. She is too young for the new medications that's been approved. The hydroxyurea causes her to have increased hair shedding and white blood cell counts to get elevated. Praying for a medication that will help her quality of life.

Sincerely,
Cierra E.

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

cierraedelen@gmail.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Amy K.

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Family member or Caregiver in the sickle cell disease community.

Briefly introduce yourself:

I am the mother of a child with sickle cell SS.

Please discuss your SCD Story:

He was diagnosed at 8 months of age. He is comparatively healthy, but he still deals with pain that we treat at home whenever the weather changes, which is often because of where we live, and when he is otherwise feeling sick. He has a major pain crisis maybe once a year. He is still young (9), so we know that this will increase as he hits puberty. Right now fatigue is a big issue for him. He has trouble keeping up in school and requires an IEP to track with his classmates. He misses class because of pain, fatigue, doctor's appointments, etc. It is very hard for him emotionally because he can't go to recess with his classmates, almost all the time, or participate in common sports and activities. He feels very isolated and can be withdrawn. We have had to spend large amounts of time and money on counseling because he developed such severe anxiety and battles feelings of sadness and isolation. Sickle cells dominate so much of what we can do and where we can go as a family, mostly because of the weather or concerns about fatigue. My husband had to forgo a job opportunity because the altitude where we would move was too high for our son. That inability to move resulted in a period of unemployment that severely impacted our savings.

Please discuss any experience with chronic pain:

I can tell you what pain sounds like- it is horrible. I wish that anyone who thinks that there is a cold calculation to be made about the cost of a drug vs the cost of a hospital stay would have to sit through a pain crisis while the doctors scramble to find the right dosage and the morphine runs out a full hour before they can give more and you have to spend all night listening to intervals of wailing and screaming every two hours that are so gut-wrenching and terrible that the charge nurse comes to you in the morning and tells you that even she was fighting back tears and she doesn't know how kids with sickle cell survive it. It costs dearly to spend a night listening to that pain. I can't imagine what it costs to experience it.

Please discuss any experience with management of sickle cell pain at home:

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
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He has maybe three or four pain episodes a year that require narcotics, but are manageable with what we can administer at home (along with heat, rest, fluids, etc). He also has more minor episodes that we manage with ibuprofen, heat, rest, fluids, and those are maybe once a month, more when the seasons change. We usually only end up at the hospital for pain once a year. We are super careful about triggers, and that has drawbacks too- it limits my son to try and avoid pain.

Please discuss any experience with fatigue:

My son doesn't have a regular amount of energy, he is very quiet and reserved compared to other kids in his grade. We are certain that sickle cell has an impact on this because the few times that he has had a transfusion we notice a major uptick in energy immediately following as well as a more engaged and playful personality. His fatigue limits everything- where we can go, what he can do, his school work, engagement with friends and family, etc.

Please discuss any experience with other complications:

It is very expensive to have a child with a chronic illness. We spend so much more on his medical care than any of our other children. Also, it will be very hard for me to get a full-time job when all of the kids are in school because of the demands of his medical care- this includes the demands on my time of obtaining referrals, trips for blood draws, dr appts, yearly TCDs, ER visits for every fever, the added complications for every other non-scd related illness- he had sleep apnea and a hernia and he had to be hospitalized for both surgeries in a hospital that was much further from our home. The finances- both what we spend on his medical costs, plus the opportunity cost of my not being able to seek full time employment impacts everything our family does, including savings for important things for our son with SCD and our other kids. We have very little saved for college, my other kids can't participate in things they want to do because we need to keep money free for medical costs. Additionally it is very stressful to have a child who can go from healthy to desperately sick in a short period of time. You never know when things will go south, and you know any plans you make need to be changeable. For example, my son seems to get sick often right before we travel to see family at Christmas, so we can never book inexpensive non-refundable tickets- we have to pay more because we know there is a good chance we will have to change plans (and this has happened).

Please discuss the unmeasured costs of sickle cell disease:

Last month wasn't too bad, I think maybe \$20 on ibuprofen and all the money for the extra juice and things I buy him to coax him to stay hydrated, but the month before we had two ER co-pays when my son got sick, so that was \$150 each. Additionally, I paid a hospital bill from an operation that would have been a \$50 outpatient charge had he not had sickle cell, but since he did required multiple days at a hospital and cost us \$400, and then \$30 in parking fees and the cost of food during his stay. Additionally, he required tami-flu to treat his illness, but I forget how much that was. Honestly, getting hit with \$300 right before Christmas was so bad I didn't even pay attention to the co-pay for the medicine. The cost of therapy must be added in as well. \$25/session co-pay, my son now goes every week, but for years he had to go weekly. Whatever is on the insurance bill is only the tip of the iceberg for a hospital stay- parking, food, food for the rest of the family when mom isn't home to cook, the difficulty of finding babysitters or else dad has to miss work (which is extremely stressful on everyone while also dealing with a medical crisis).

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Please discuss the impact of stigma and discrimination:

It means that sickle cell doesn't have the funding it deserves relative to other diseases. It means that doctors under treat pain, question your diagnosis, and make you wait around because they think your condition isn't serious enough to triage quickly. It means having to answer questions about the value of the pain of the sickle cell community so that people can access life-improving treatments. It means knowing that when there is a cure it will probably not be covered. It means watching warrior after warrior die decades too early because they developed complications during hospital stays, and having to fill out questionnaires to justify giving people with sickle cell disease medicines that would help avoid hospital stays and therefore save lives.

Please discuss the impact of hospitalizations:

It would mean a huge improvement in our quality of life, and a big reduction in our expenses. Most importantly, it would mean that my son was not experiencing horrific pain, and that would be priceless.

Please provide any comments about the current or new treatments for sickle cell:

My son has naturally high fetal hgb so HU hasn't been recommended. We tried Endari but then our insurance decided to stop covering it. It seemed to help but it did also seem to cause headaches. I still think it would be worth it to be on it, but we can't afford to pay out of pocket.

Sincerely,
Amy K.
amyk105@yahoo.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Brandy McGowan

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

I'm a 29 year old female living with sickle cell anemia-SS in southern MS.

Please discuss your SCD Story:

I was diagnosed with sickle cell at birth. Sickle cell feels like a never ending marathon of hurdles and obstacles that I'm constantly faced with that prevent me from living my life to the fullest. The hurdles are pain crises, depression, surgeries, chronic pain on a daily, extreme fatigue, stigmas, avascular necrosis, a mountain of complications and the list goes on and on. I experience complications from sickle cell daily, if it's not a pain crisis then there are the aches and pains, of not the aches and pains it's the withdrawal symptoms from constant pain medications.

Please discuss any experience with chronic pain:

A sickle cell pain crisis in my opinion is a multilevel pain wave that attacks your body randomly without cause. There's the first sign of pain that comes which let's your body know this is a full blown crisis, the real deal not your typical ache. It's a spine gripping, pulsation that runs through your entire body. You can try to conquer it with oral meds to prevent it from going further but there's really no use. Secondly there's the wave that goes specifically to its target areas and makes itself a home. This could be your back, legs, chest, arm, wherever. This stage almost always requires hospitalization. This pain feels like a hot lava coursing through your veins and joints. This pain is typically the peak of the crisis. The pain doesn't respond to ANY oral meds, and sometimes is rarely controlled by high dose IV medications in the hospital. This pain can last anywhere from a day or two to several weeks. Lastly there's the third phase of the crisis when the pain finally is controlled and slightly subsides. You can function a little better now, resume some ADLs but you're still hurting. This pain is a constant ache to remind your body of the turmoil it's just survived, until next time. You may require physical therapy to help your restore some function in your limbs that have been attacked by pain so long they forget their function other times, you just resume life as best you can.

Please discuss any experience with management of sickle cell pain at home:

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Last year I had a total of maybe 10 pain crises, of which 2 required hospitalization. I try to manage as best I can at home with remedies to simply avoid the stigma often placed on sickle cell patients. It's sad that I don't want to seek treatment simply because I don't want the hospital staff to see me too often and even get the notion that I'm a drug seeker. Therefore I work as closely as I can with my treatment team(primary care physician, pain management specialist, and hematologists, orthopedic surgeon) to create a regimen to keep me as healthy as possible and give me the meds I need to treat myself at home. I utilize heating pads, massage therapy, different creams and rubs topically, hydrate hydrate with water and natural juices, hot baths and try to sleep as best I can. Home treatment usually takes a week to resolve a pain crisis.

Please discuss any experience with fatigue:

I AM TIRED 24/7!!! I wake up tired, I go throughout my day exhausted, I go to sleep tired and I can never get enough rest. It's frustrating trying to explain this to friends or family that doesn't understand and think that you're just lazy. No, my body is basically failing me. On top of fatigue I also suffer from insomnia. Fatigue limits what I can accomplish in a day, I usually wake up and set out to accomplish at least one task may it be laundry, grocery shopping, a few errands. It's discouraging. I try to combat my fatigue with vitamins and supplements but what can you do when you're severely anemic every day of your life.

Please discuss any experience with other complications:

Avascular Necrosis of my joints. This condition stems from bone not receiving adequate blood flow or vital nutrients to stay healthy and alive, therefore the lack of the aforementioned causes bone deterioration and collapse. This has been a new condition that I've been battling for last five years. I've had a total hip and a total shoulder replacement and now require another total hip replacement of my remaining natural hip. These surgeries require substantial downtime to recover fully and that in itself impacts my life greatly. I want to return to my career, further my education, and resume my life. All of my goals have been put on hold due to this condition along with sickle cell anemia and it's symptoms. I've attempted to return to work but with joints deteriorating and constant pain my functioning in the workplace is limited. I can't start my masters degree because I don't know when I will be sick, or when another joint will collapse requiring surgery. My life is an ongoing battle of constant pain and setbacks.

Please discuss the impact of hospitalizations:

I typically only go to the hospital for treatment maybe once out of the year. Before my most recent hospitalization last year, I hadn't been to the hospital in 5 years. I thank God that I am as blessed as I am to manage my sickle cell as well as I do. However when a portion crisis is severe enough for hospitalization, my stay is always uneventful. I almost always have a treatment team that's understanding and sympathetic to my illness and understand what I'm going through. Living in southern MS one may expect discrimination or maltreatment from medical staff but that is not the case. I've never been treated no other way than with compassion and care. I thank God daily for this because it is rare in our sickle cell community.

Sincerely,
Brandy McGowan
bmcgowan20.bm@comcast.net

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Dennis McCullum

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

I am a 63 year old male with Sickle Cell Disease, hemoglobin type (SS), having a bachelor's degree in Accounting. I've worked for major corporations such as U.S. Steel, Arco, Kraft and Baxter in the Finance and Systems for 20 + years. Managing both daily (family, work, social) life events and controlling stress level. Throughout these years, there were Sickle Cell crisis events that brought attention to corporate America of what Sickle Cell Disease was and how strategically to best optimize our work relationship.

Please discuss your SCD Story:

I am the second of five children in my family to have Sickle Cell Disease. My older brother, by two years, also had Sickle Cell Disease (SS). He lived to be three years old, when I was one year old, where he succumbed to complications of Sickle Cell Disease, along with double pneumonia and spinal meningitis. This altered our whole family dynamic, in that now there was increased attention on myself and probably less attention given to my other siblings at the time. My life and it's anomaly, spread throughout our family hierarchy, through extended family and friends, because at this point EVERYONE had to know that I had Sickle Cell and what the do's and don'ts were and what I could and couldn't do in association with playing and school. I was told numerous times that I had limited time on this Earth, my estimations were 12 years old, 14 years old and 18 years old. What goes through a CHILD'S head when they hear that they're going to die at 12 years old? How is this event going to happen will I just fall dead, will it be a crisis event or a stroke or heart attack? No one could answer this question, not even the doctors! So, after these three non-death events didn't occur, my perspective on my life could either go one or two ways, I could live a reckless fast life, throwing all caution to the wind or normal structured life of a normal person with stages of life events, like turning 30, 40, 50 years of age till the wheels fell off, no anticipation of a early death, I chose the latter. There were numerous Sickle Cell crises, that felt like stones in an hourglass, that stopped the flow of everything that could pass through the smaller passage including the sand and was felt with each and every subsequent heartbeat. The pain is so intense that I would intentionally strike the good wrist against the hospital bed railing to cause enough pain to distract my mind from fully realizing the pain emanating from the sickling wrist!

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

As I grew older and wiser, I learned that stress was a frequent trigger to my Sickle Cell crisis. So, my new normal was to have a nonchalant, laid back point of reference to everything, because even happy stress was a deterrent to my joy of traveling, missed three trips to Africa because of anticipation and the exuberance of my journey! Fatigue was and is a constant drag on a lot of normal men activities football, basketball, swimming and track. I was relegated to mental stimuli such as cards, backgammon and chess. So, in short Sickle Cell alters many life goals!

Please discuss any experience with chronic pain:

Sickle Cell pain crises feel like a drum beat that with each heartbeat there's a surge of sharp objects trying to get through your smallest opening in an hourglass. As far as things a Sickle Cell patient can't do there are plenty, but there are many things that this obstacle can turn into an opportunity, so one should try the things you desire and find out if it definitely works against you or is the case for someone else.

Please discuss any experience with management of sickle cell pain at home:

Managing pain at home is like defining a new normal that you have to just get used to, because it will probably be around ALL THE TIME. It's like being strapped to a ball and chain for life, it's a drag some days and some days one can carry on like a champ! In my younger days I was admitted frequently, but as I grew older and wiser, I was able to cut down on admission because I learned to cut down the effects of STRESS in my life. And that would be my hope that every patient would learn to reduce the STRESS in their lives and live a healthier and productive life. A patient's perception of pain is quite different than the hospitals staff perception of pain, if you think your level is at a 10, they will perceive it to be a 5 and cause you to sit in the emergency room for extended amounts of time while someone with a simple cold gets in before you, this aggravation would cause patients to wait it out at home waiting hopefully for the pain to subside to a level that you can tolerate.

Please discuss any experience with other complications:

Being a 63 year old male with Sickle Cell Disease and being exposed to the everyday lifestyles of a lot of Sickle Cell patients sometimes I have "Survivor's Remorse", when a patient passes on for initially going to the hospital in crisis and then it turns much worse. These things affect Sickle Cell patients across the globe, when one dies you always wonder "Who's next", if not me will it be someone very close to me in the Sickle Cell community.

Please discuss the impact of stigma and discrimination:

There are many "stigmas" about Sickle Cell Disease, it's a black disease, we're drug seekers, blacks can take more pain than whites, you don't look or act sick and then on the opposite end you're showing out, you're over the top, it can't be that bad, so as a patient you are damned if you do and damned if you don't! And yes there is discrimination, my own episode is when I got sick in an affluent white neighborhood where I worked and had to be taken to a local area hospital (white) and I was in my 40's years of age and I informed the staff that I was a Sickle Cell patient. Would you believe they tested me for Sickle Cell Disease and I didn't know until I received my bill from the hospital, in which I immediately disputed the charge and they apologetically removed it!! Why would a 40+ year old man say something like that without it being unequivocally true! I was amazed and appalled!

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

A disease that has been around for over a hundred years is just now getting medical treatments and therapies discovered, that's an insult and slap in the face of how important the medical and pharmaceutical industries think we are as a priority!

Please discuss the impact of hospitalizations:

I have been re-hospitalized after being driven a mile from the hospital I just got discharged from twenty minutes ago!

Sincerely,
Dennis McCullum
dennis_mccullum@yahoo.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Elisha D

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Family member or Caregiver in the sickle cell disease community.

Briefly introduce yourself:

I am the mother of a 4 year old little girl with Sickle cell SS.

Please discuss your SCD Story:

She was diagnosed shortly after birth. She is relatively healthy, because I ensure she has a healthy diet, stays hydrated, and gets plenty of activity and rest. She still has to take at least 3 medications everyday to manage her disease. Luckily, I am a registered nurse and very capable of managing her care, however, it can still be exhausting. As she has gotten older, she has begun to experience a pain crisis. Due to pain crisis and routine disease management, she has missed several days of school and I have missed several days of work.

Please discuss any experience with chronic pain:

It is absolutely devastating to watch your child cry out in pain. She describes it as a sharp pain that beats like her heart.

Please discuss any experience with management of sickle cell pain at home:

We are only beginning to see her crisis. She has had 2 this year. One was managed in the hospital with IV meds. The other at home with tylenol and motrin around the clock. I try to manage pain at home because of the risks of her being exposed to other illnesses that could complicate the situation.

Please discuss any experience with fatigue:

Luckily she has the energy of a typical 4 yr old. When she becomes fatigued, I immediately know there's a problem. I, however, am constantly tired. As a caregiver, and full time worker, I have had to get used to this feeling.

Please discuss any experience with other complications:

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

We are definitely impacted financially, even with health insurance, we still have to come out of pocket for medications and hospital visits.

Please discuss the unmeasured costs of sickle cell disease:

I've probably spent \$400 on SCD last month. I have spent hours on the telephone with insurance companies, during work hours. I have missed at least 2 days of work this month due to appointments and a pain crisis she had.

Please discuss the impact of stigma and discrimination:

I am a nurse and it astounds me how many medical professionals lack basic knowledge about sickle cell patients. I've often overheard conversations about how they are addicted to pain medications. I've also heard frustrated medical providers complain about how noncompliant patients and families affected by SCD are. Though I have witnessed instances where these circumstances are true. This perception hurts us.

Please discuss the impact of hospitalizations:

I would love decreased hospital visits. For now, my child is very familiar with the hospital and relatively comfortable going, but it is draining on me as a parent; worrying about her health and managing other obligations.

Please provide any comments about the current or new treatments for sickle cell:

We focused on a healthy diet initially. She also was placed on antibiotics as an infant. We have added Hydroxyurea to the regimen in the last 2 years. Overall I believe her treatment is effective for now.

Sincerely,
Elisha D
Elisha_c11181@yahoo.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Brittany Hightower

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

In Brittany. Founder of Slay The Sickle Cycle a job run by myself, an independent sickle cell advocate who provides advocacy, education, and awareness of sickle cell. I volunteer for other foundations such as the red cross and I help feed the homeless and the hungry through my own organization that I want to one day have 501 c 3 status. I'm a poet, writer, speaker, and entrepreneur. I Will soon be a published author of a book of poetry about my sickle cell journey. I hope to continue to encourage and advocate for those like myself who otherwise would have no support. My purpose in life is to use my life as a guide to help others and I have made my God proud.

Please discuss your SCD Story:

I was diagnosed with sickle cell anemia SS disease at birth. Sickle cell disease feels like superman is lying on top of me while I'm being stabbed by a joker and shot by dead shot..who never misses, simultaneously. It hurts extremely badly, I feel deprived of oxygen and energy all the time. I'm always in some amount of pain no matter what. I'm often in the hospital with severe crises. My daily life is negatively impacted by sickle cell. I can't work the way I want because I'm sick and in pain too much so I have had to become an entrepreneur. Which is a bit ironic.

Please discuss any experience with chronic pain:

Like i said before I feel like someone or something is lying on top of my chest and won't move. My breathing is impaired and I have chronic fatigue. This is pretty much all day every day no matter what and when I'm in crisis it's the same but multiplied by 10. My entire life is impaired by this. I have been let go from every single job I've ever had. I've had to drop out of school because I'd be too ill to concentrate and keep up my gpa. It's hard to go out with friends or show up at scheduled events. I missed my very own 30th surprise birthday party because instead I woke up in the icu. I was never able to participate in school activities and that hasn't changed in all my years of living.

Please discuss any experience with management of sickle cell pain at home:

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

I manage my pain at home with long and short acting pain meds around the clock as needed. Within the last year I've had too many crises to count. If i had to guess id say i have at least one crisis a month or every other month. Of those crises at least half result in hospitalizations. Sometimes though my pain is bad enough I don't go to the hospital for treatment because it's too taxing on my well being and actually makes the situation worse because of the treatment we receive as a result of having scd.

Please discuss any experience with fatigue:

I experience chronic fatigue. It's a 7-10 out of 10 usually. It impacts my quality of life by preventing me from having the energy to participate in activities or life in general.

Please discuss any experience with other complications:

Sickle cells impact every area of my life. Even my personal relationships. I have children, school, work, finances, and my mental state.

Please discuss the unmeasured costs of sickle cell disease:

I have missed the majority of my entire life due to sickle cell disease. I can't work enough to pay for the minimum cost of living. I have even been homeless. Now I use my disease as fuel to help others which has in turn saved my life.

Please discuss the impact of stigma and discrimination:

When it comes to sickle cell we are stigmatized as being drug seekers and discriminated against because of it. Race has a large effect on our level of care. Because it's a predominantly black disease we are undertreated, underrepresented, and no where near understood. Our access to treatments, research, and necessary care range from bare minimum to total non existent. It's So sad to even talk about.

Please discuss the impact of hospitalizations:

It would mean the world to me to reduce hospitalizations because i would actually have a chance at a real life. When I'm in the hospital I view my life as a complete waste. I'm not able to be productive and once I'm discharged,like a cycle it happens again and again. I have been rehospitalized after discharge because I wasn't treated right the first time. That's why I want to Slay the Sickle Cycle! It's self explanatory.

Please provide any comments about the current or new treatments for sickle cell:

I've tried pain management with different meds. I've tried hydra, scheduled blood transfusions monthly. Thus far the only effective method is pain management with long and short acting drugs on an as needed basis. I am in the process of starting one of the new drugs named Adakveo (crizanlizumab) and I hope it has a great impact.

Sincerely,
Brittany Hightower
Slaythesicklecycle@gmail.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Lyndsey R.

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

I am 31 years old and live in NC. I have sickle cell SC but I do not let it stop me. I work out 5x a week (dancing and weight lifting) and I travel the world as a pharmaceutical consultant.

Please discuss your SCD Story:

I was diagnosed at birth but my earliest memory of an SC crisis is in preschool. I am blessed to not have frequent hospitalizations but I do have retinopathy in both eyes and AVN in multiple joints.

Please discuss any experience with chronic pain:

My daily pain can be ignored for the most part; they are probably around a 1-2 on a pain scale of 10. My crises range from 3-10 and can last from 1 day to 2 weeks. I usually describe my pain as being hit or run over by a truck. I have the bigger crises maybe 1x a year. I have missed many days of school and work due to SC pain crises and have had 3 surgeries that took me out of work for 6 weeks each time. I avoid swimming, cold weather/rooms, and physical activity in hot weather to prevent my symptoms. I try to drink a gallon of water a day and stay well rested.

Please discuss any experience with management of sickle cell pain at home:

To manage my pain at home I start off with a heating pad, OTC medication, rest and hydration. I'll move on to my prescription oxycodone if pain doesn't subside and will go to the hospital once my pain reaches a 7-8. Listening to my body and taking care of it allows my infrequent hospitalizations.

Please discuss any experience with fatigue:

My level of fatigue goes up and down. I can be full of energy one minute and exhausted the next. My family and friends are accepting and let me rest and sleep when I need to without getting upset.

Please discuss any experience with other complications:

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

As I grow older, my anxiety of having a stroke increases. I am also afraid my pain frequency is increasing and my retinopathy progressing as I age. My medical bills are ridiculous too. I have come to the acceptance that I probably won't ever pay them off; they'll just keep increasing.

Please discuss the unmeasured costs of sickle cell disease:

I have missed 18 weeks of work due to SC surgeries (1 core decompression, 1 hip replacement, and 1 shoulder replacement) and countless days of work and school due to pain crises. My hospital bills increase every year and I have been on a payment plan with Duke Hospital for years. I spend a lot of money on bottled water every month to ensure I can stay hydrated while I am on the go.

Please discuss the impact of stigma and discrimination:

Luckily for me, my hospital network is a sickle cell department. My medical charts have instructions for ER doctors for my treatment and when I go to the hospital my hematologist is always alerted. I don't think I have been discriminated against for having SC but I am more aware of the amount of people (medical professionals included) that do not know about it. I make all of my medical providers (OBGYN, dentist, orthodontist, chiropractor, etc.) know I have SC so they can adjust my car as needed and I will find another provider if I feel like they lack the knowledge I feel like they should have.

Please discuss the impact of hospitalizations:

Hospitals are no fun. I try not to go unless it is absolutely necessary. There have been 2x that I can remember being released from the hospital only to have to return the next day. I don't know if that is the fault of my own for wanting to leave due to money worries or the doctor for not insisting I stay until my blood levels are correct.

Please provide any comments about the current or new treatments for sickle cell:

I haven't tried any new medical treatments for SC but I do participate in medical surveys and am always on the lookout for clinical trials that I qualify for.

Sincerely,
Lyndsey R.
lynnylu315@gmail.com

DayShana Jones

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

My name is DayShana most people know me as Sugalump. I am 28 years old and I was diagnosed with sickle cell SS at birth. I have a three year old son Tristan. I am a cosmetologist and have been working as a stylist for the last ten years.

Please discuss your SCD Story:

I was diagnosed with sickle SS at birth. Living with sickle cell disease I experience pain every single day of my life for the last 8years. The pain is not always bad , but when it is it's very unbearable. It feels as if nails are scraping against my bones back and forth. I can't even live a normal life living with sickle cell disease. Although I work 6days a week, somedays I'm not able to make it. At times the pain gets so bad I'm not able to care for my child. That's what hurts the most. Not being able to care for your child because you have an illness that's taking over your life. Can you imagine?

Please discuss any experience with chronic pain:

For me as I've stated my pain gets so unbearable so excruciating it feels as if nails are driving through my bones back and forth , and back and forth again. Some days I'm not able to make it to work. Some days I'm not able to interact with my three year old. I refrain from all physical activity because I'm scared that I'll have a flare up.

Please discuss any experience with management of sickle cell pain at home:

I try to manage my pain at home as best as I can. I've had so many crisis last year I'd need more than two hands to count. Just about all of those crisis I ended up in the hospital. A lot of time I try not to come to the hospital to manage my pain because there are some who either don't believe that not just me but sicklers as a whole have pain because we look so normal. Another reason why I don't wanna come to the hospital is because I live most of my life in the hospital and I hate being here.

Please discuss any experience with fatigue:

I'm always extremely fatigued and exhausted

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Please discuss any experience with other complications:

Dealing with sickle cell disease I deal with depression & stress. It also effects me financially. I miss a lot of work from being in the hospital I'm always having to catch up on bills child care etc.

Please discuss the unmeasured costs of sickle cell disease:

I have an overflow of costly hospital bills. In the last 30days I have worked 5 out of the 30 days.

Please discuss the impact of stigma and discrimination:

We are discriminated against living with sickle cell disease because it mostly affects Africa Americans. They label and stereotype us as "drug seekers " because we require pain meds. We could have better care and better treatments but because of our color we get mistreated.

Please discuss the impact of hospitalizations:

To reduce hospital admissions by one is a start. Being in the hospital is very stressful and depressing and yes I have been re admitted to the hospital for 30days.

Please provide any comments about the current or new treatments for sickle cell:

Yes I've tried several treatments and no they haven't worked for me.

Sincerely,
DayShana Jones
Jdayshana@gmail.com

Public Comment to ICER's Draft Evidence Report: Sickle Cell Disease
Patient Advocate Responses

Nic K

February 20, 2020

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

RE: Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear ICER,

Please see my feedback regarding ICER's Draft Evidence Report:

I represent a Patient in the sickle cell disease community.

Briefly introduce yourself:

I am a 9 year old boy with SS

Please discuss your SCD Story:

I was 8 months old. When. You have sickle cell it makes things a lot harder, like when you get a shot and you start hurting a ton. Everything hurts more than it does for other people. You can't go outside because it is too hot or cold. It makes me feel like I can't play with my friends because I have to stay in.

Please discuss any experience with chronic pain:

Sickle Cell pain hurt so much. It is the worst feeling I have.

Please discuss any experience with fatigue:

I feel so tired. I can't run that fast. I can't play like my friends. I want to run fast in baseball, but I can't.

Please discuss the impact of hospitalizations:

I would feel so good if I didn't have to go to the hospital as much. I don't like to get all the shots. It makes me so unhappy. I have to miss out on so many fun things.

Sincerely,

Nic K

amyklug105@gmail.com



February 20, 2020

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Evidence Report “Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value”

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with life-threatening and altering conditions and chronic diseases for them to have access to vital therapies and services. Access to life improving treatments and services are essential for those people, and it spans affordability, insurance coverage, and physical access. To support improved access, we are committed to engaging patients, caregivers, physicians, media, health policy experts, payers, providers, and others to foster realistic, patient-centered, solution-oriented discussions about the entire U.S. health care system. That is, our goal is a balanced dialogue that illuminates the truth about health care in a just and equitable way.

We appreciate the opportunity to provide our comments on ICER’s January 23rd draft report, “Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease.” Our comments about the draft report are organized below into sections concerning: Patient and Caregiver Perspectives and Issues; Importance of New Treatments for Unheeded Diseases; Problems of Completeness and Timeliness; Assumptions; and Additional Points.

Overall, we concur with the draft report’s statements that “a broad appreciation for the impact of SCD on the lives of patients and their families must be achieved and must be kept front and center when making judgments about the value of these treatments.”ⁱ And “What is certain, however, is that the introduction of new, effective treatments for SCD serves as an opportunity for the overall care of patients with SCD to be re-imagined and improved from top to bottom.”ⁱⁱ We strongly hope that ICER and its advisors deeply embrace those concepts as part of the fundamental value of the new treatments for SCD.

Patient and Caregiver Perspectives and Issues

We appreciate ICER’s thoughtful description of SCD’s impact on people’s lives – both patients and their caregivers – in the Background and Patient Perspectives sections. We also applaud ICER for improving its standard operating procedure to include a Patient Perspectives section in all its reports moving forward.

We share ICER’s concern about the lack of information about quality of life (QoL) data from the clinical trials ICER reviewed for the draft report. We would have appreciated more discussion

about whether that lack of data – or findings of non-significant improvements in QoL measures in the clinical trials – are due to methodological problems with the trials, problems with the measures used to evaluate QoL, or some other factors. We are hopeful that the survey ICER, Sick Cells and the Sickle Cell Disease Association of America (SCDAA) are conductingⁱⁱⁱ will provide greater insights into how to better measure QoL for people with SCD and their caregivers. (See more about this survey below.)

We concur with the draft report’s statement that new treatments hopefully “will allow students to attend more school, will decrease the number of missed days from work, will have fewer demands on the caregiver, and will have lower out-of-pocket costs.”^{iv} We similarly concur with the draft report’s statements that “It also seems likely that new, effective treatments could reduce caregiver burden,”^v and “if patients have less pain, suffer fewer morbidities, have fewer hospitalizations, and need fewer doctor visits, then their families and caregivers would have more time to focus on their own education, careers, family, friends, and other interests.”^{vi} Given those forward-looking statements, we hope that the survey being conducted will have appropriate questions and be methodologically robust enough to provide valid insights on those issues.

We find the draft report’s discussion about variability in the severity of SCD to be very important, and appreciate the draft report presenting information about people who have more or fewer acute pain episodes. As the report also notes, determining benefits of specific treatments will always require individualized assessments, but until there is more data “the alignment of costs with potential patient benefits for these new therapies is unclear.”^{vii} That is why we strongly believe that decisions about individual treatment plans are best done using shared decision making by people with SCD and their care team.

Related to individualization of care, we are a bit concerned that the draft reports analysis and methodology does not adequately consider or address the complexity of SCD’s multi-organ system manifestations in an integrated manner since that is the reality for people with SCD. That is, people with SCD do not address their disease in a piecemeal or siloed approach, but rather need whole-person care and considerations from their care team. Another important patient perspective that is not adequately discussed in the draft report is the different routes of administration, i.e., IV v. oral. Those difference can dramatically affect patient costs and access, particularly since IV administration may require travel to a clinician’s office. We would appreciate ICER more extensively exploring those issues in the final report.

Importance of New Treatments for Unheeded Diseases

As the draft report notes – and we concur – the population primarily affected by SCD has been marginalized in many aspects of health care in the United States, ranging from access to treatment, to financial support for public health and research. Therefore, we are gratified that the draft report highlights the importance of new treatments for SCD and how these new treatments will help reduce inequity in treatments. Hopefully, the availability of new treatments for SCD will illuminate this issue and foster further discussions leading to more research and better treatments for diseases that disproportionately affect populations that have been underrepresented in access and funding in our society.

Despite the historical situation, we are heartened that these new treatments for SCD are now available, and that many more are on the way, with about 30 potential sickle-cell drugs in late-stage development,^{viii} including at least one potentially curative gene therapy.^{ix} However, we are concerned that if reimbursement or access to the recently approved treatments is problematic, that will result in resources being diverted away from clinical trials and thus delaying or killing the development of new treatments. Such an outcome would of course perpetuate the historical marginalization of the people and families affected by SCD, and continue society's disregard for the health care needs of SCD patients and families, and potentially other similar diseases.

The draft report notes that the availability of multiple new medicines with different MOAs “provides an opportunity to potentially combine therapies to address multiple pathophysiological pathways as opposed to just one. While there is much to be learned about the potential benefits and harms of combination therapy, there remains significant potential for new understanding and hope for additive health benefit for patients. With these new treatment options, a more targeted approach, and the potential to deploy multiple concurrent therapies, comes the potential for a healthier patient.”^x We believe it is very important to explore this likelihood since the trend in modern medical treatment is the use of multiple medications, and the two new treatments also provide different clinical benefits to patients, e.g., as shown in Table 5.24^{xi} crizanlizumab reduces acute pain crisis events, and voxelotor reduces incidence of strokes.

Problems of Completeness and Timeliness

While we applaud the survey that is being conducted with Sick Cells and SCDA, we are extremely concerned that ICER released the draft report for comment before the survey results could be included. This is another indication that patient perspectives are an afterthought and a third-tier priority for ICER's analyses and evaluations. We find this particularly problematic since the draft report even states that the survey “may provide valuable information needed to assess the comparative effectiveness of the interventions and help us to better quantify important information on quality of life and productivity.”^{xii} If that is the case, then why not delay the draft report so those results could be included?

We are also a bit concerned about the methodology of the survey since we understand that it was conducted using SurveyMonkey where anyone could provide responses rather than using a curated and validated source list for obtaining responses. Please respond as to how the survey's methodology will provide useful, valid and robust insights to ICER and SCD stakeholders.

Similarly, we question to rush to release the draft evidence report rather than wait until the Budget Impact Analysis (BIA) is finished and available for comment. Presenting the draft report without the BIA precludes public comment and input. We did not see changes to the presentation of the BIA in either the proposed or final updates to ICER's 2020-2023 value framework documents. Will ICER's new standard operating procedure be to NOT include a BIA in draft evidence reports? Does ICER believe that public comment on their BIA is not important or relevant? Given that decisions about coverage and benefits are not made until the middle of the year – or later – for the following year, we do not understand the need to produce the final report by mid-April^{xiii} when a month or two later would provide more useful information to the stakeholders ICER is seeking to influence, e.g., payers planning their next year's formulary

structure and access protocols and premiums. Please explain and justify not including the BIA in the draft report and declare what the policy will be moving forward.

Assumptions

While the population of people in the U.S. with SCD are mostly covered by Medicaid and Medicare^{xiv} we are concerned about the use of the Truven database since it is almost entirely commercial claims.^{xv} And further, it was reported at the 2017 American Society of Hematology Annual Meeting that “Patients with sickle cell disease (SCD) who are insured through Medicaid used hematology care services at a far lower rate than commercially insured patients.”^{xvi} And that “Medicaid patients also exhibited greater emergency department (ED) use and lower compliance with hydroxyurea (HU) treatment.” Therefore, please explain how the use of a commercial database to model SCD patients care and utilization makes sense and does not invalidate the draft report’s conclusions – or at least make them highly suspect as to their magnitude and accuracy.

Four other assumptions that we request ICER explain further are:

- The baseline utility for uncomplicated SCD in Table 5.16 cites reference #96, but that document is about care guidelines for people hospitalized with SCD in the U.K., and we do not see any reference to utility factors or calculations. Please clarify the source of the utility factor of 0.71 show in Table 5.16.^{xvii}
- One of the significant challenges of comparing different treatment options is comparability across data sets derived from different clinical trials done at different times and often with different criteria and protocols. The draft report notes the very different withdrawal rates for people in the L-glutamine trial evaluated – despite low rates of adverse events.^{xviii} This raises significant concerns about data validity despite attempts to correct for any skewing.
- Assuming that the risk of heart failure and myocardial infarction is the same as pulmonary hypertension^{xix} is questionable. ICER should present some data – or at least expert opinion or consensus to support such a broad assumption.
- The draft report states in the Limitations section: “In addition, a number of assumptions had to be made about how to combine risk factors and dis-utilities for patients experiencing multiple acute and chronic conditions. These assumptions were described previously and the justifications described.” ICER needs to provide citations and references for those assumptions and justifications. Not doing so is opaque and flies in the face of transparency.

Additional Points

- Given that the three new treatment options for SCD have different MOAs – and it is very possible that some people with SCD will benefit from simultaneously using more than one of them – we appreciated ICER including in its disclaimer on page iii that “data inputs to ICER models often come from clinical trials; patients in these trials and provider prescribing patterns may differ in real-world practice settings.”
- We appreciate ICER noting that treatment for SCD in the U.S. is “highly variable,”^{xx} but we would be remiss if we didn’t note that this is true for most diseases in the U.S. Therefore, stating that the variability of care for people with SCD “represents a failure of the US health care system” is too myopic because that variability - and this type of “failure” is a systemic situation in U.S. health care rather than a particular problem with SCD. For example, one article found that the consequences of that dysfunction is that 14-16% of health care spending

in the U.S. may be directed towards such variability in care that is inappropriate or not useful.^{xxi}

- The final report should talk about geographic differences in SCD prevalence across the U.S. since this may be important both for costs and modeling purposes, as well as informing different stakeholders – including regional and local payers.
- On page 16, we would suggest editing the statement “ICER now includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets,” by inserting the word “fixed” before “health care budgets” since if such budgets are not fixed or predetermined – such as with the U.S. Veterans Health Administration, – then the concept of headroom is inconsistent, e.g., for entitlement programs such as Medicare or Medicaid there is no fixed annual budget, so spending literally cannot run out of headroom.
- In the Patient Perspectives section there are no attributions for the quotations. While we recognize that identifying the individuals who provided those quotes may be inappropriate, we also strongly believe that some indication of the type of person and source of the quote would make them much more meaningful, and add to the transparency and validity of ICER’s efforts. For example, we think three pieces of information would be appropriate:
 - Identifying the quote as coming from a person with SCD, a caregiver, or a clinician;
 - Their age (or age range), age of the person with SCD they are a caregiver for, or for clinicians their practice setting; and
 - Source of the quotation, e.g., focus group, public meeting comment, letter/email, personal conversation or similar communication directly to ICER.
- Page 17 – “People with SCD often end up on formal disability programs.” This needs to be defined, since we are unaware of what would qualify as an “informal” disability program. We recommend this sentence be more specific, and include data and examples of disability programs.

Conclusions & Recommendations

While we recognize the draft report’s thoughtful discussion about the severity of SCD for patients and caregivers, and the general undertreatment of people with SCD, Patients Rising Now believes that ICER’s Draft Report on the new SCD treatments is incomplete by ICER’s own standards, e.g., the survey of patients and caregivers is not complete, and the Budget Impact Analysis is missing. Therefore, the draft report should be reissued when complete. Only then can patient and caregiver comments and perspectives be appropriately included in the process. Just like the clinical dictum that the quality of care should not be sacrificed for speed (except maybe in some emergency situations), we strongly urge ICER to not diminish the validity of its attempted analysis and recommendations to fit an arbitrary and unnecessarily rapid timetable.

Sincerely,



Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

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- i Draft report, pp. 17-18
- ii Draft report, p. 51
- iii Draft report, p. 23 and <https://marylandsicklecelldisease.org/uncategorized/my-life-with-sickle-cell-disease-patient-and-caregiver-survey/>
- iv Draft report, p. 84
- v Draft report, p. 95
- vi Draft report, p. 96
- vii Draft report, p. 11
- viii <https://www.nytimes.com/2019/12/07/health/sickle-cell-adakveo-oxbryta.html>
- ix <https://www.biopharmadive.com/news/novartis-sickle-cell-drug-fda-approval-Adakveo/567471/>
- x Draft report, p. 96
- xi Draft report, p. 78
- xii Draft report, p. 23
- xiii <https://icer-review.org/meeting/sickle-cell-disease/>
- xiv Approximately 55% of people with SCD have Medicaid insurance, and another 5-10% of the 100,000 people in the US with SCD have traditional Medicare fee for service insurance. “Prevalence of Sickle Cell Disease among Medicare Fee-for-Service Beneficiaries, Age 18-75 Years, in 2016,” CMS Data Highlight No. 15, June 2019; and “Prevalence of Sickle Cell Disease among Medicaid Beneficiaries in 2012,” CMS Data Highlight No. 16, June 2019
- xv Draft report, Appendix F, p. 162
- xvi <https://www.journalofclinicalpathways.com/news/access-sickle-cell-disease-care-often-varies-insurance-status>
- xvii Draft report, p. 71
- xviii Draft report, pp 45-50
- xix Draft report, Table 5.11, p. 67
- xx Draft report, p. 10
- xxi <http://healthclarity.wolterskluwer.com/reducing-unwarranted-variability-in-care.html>

My Sickle Cell Story

Lyndsey R. 20 February 2020

Hello, my name is Lyndsey and I am a 31 year old sickle cell warrior. I was born in California, moved to Arizona when I was 4, and moved to North Carolina, where I currently live, when I was 10... all with my family (dad, mom, younger brother, and younger sister) and sickle cell hemoglobin SC in tow.

It's kind of weird having SC. I look normal on the outside but have a whole lot of stuff happening on the inside. I guess that's how most people are, but here is my SC story.

I don't know how old I was when I first realized I had sickle cell. I remember growing up like the average kids playing outside under the heat of the Arizona sun. Running through sprinklers, playing tag and red rover at the neighborhood playground, or playing on the jungle gym at the indoor play zone on the really hot days. I danced too, tap and jazz. Everything was normal. It wasn't until my parents and I started noticing a pattern between my playing activities and my pain crisis that I really understood what having sickle cell meant.

My crises would come whenever I went swimming, played outside for too long, or would go back and forth between the hot sun and a very cool air-conditioned room. Even getting really excited about something small like knowing my cousins from out of town were coming for a visit would trigger my sickle cell. "Note to self, I am not like everyone else."

Putting limits on what I could and could not do had me labeled as the "sick one" or the "fragile one" in the family. It's all jokes, I still chuckle at it to this day... it's the truth. I never knew else that was sick like me. When I was 8 and 9 years old, I had the opportunity to go to a summer camp for children with sickle cell. I met a bunch of kids there that had sickle cell, but they were all sicker than me (daily medication, frequent pain crises). I later realized that my siblings have sickle cell SC too but they never get sick. So technically, I still don't know anyone who is "sick like me."

I have been blessed to have a less severe form of sickle cell. I've had hundreds of pain crises throughout my life and I am pretty good at managing my pain at home; I prefer to wait until my pain level is at a 7-8 before going to the hospital. Hospital wait times can be quite long and the bills even longer. I have accepted the fact that I won't ever pay off my running medical tab. However, I can count the number of times that the pain was so severe that I felt like cutting off a limb or dying would be better than living.

In 6th grade I remember sitting on the floor watching TV in the living room, chilling, minding my business, home alone. BAM! Out of nowhere, I felt like a bus hit me. My back and legs were killing me! I remember my dad coming home and seeing me screaming on the floor. He hurried to get my heating pad and prescription strength Tylenol (that is all the doctors would give me at the time). Hours went by and the pain was still there so we went to the hospital. I stayed there for the night, got drugged up, and got sent home. I missed a few days of school. I remember my teachers and friends being concerned and happy for my return at the same time.

In the 10th grade I remember going the mall with my friends to pick out a dress for the homecoming dance. It was so pretty; black and white stripes with halter straps. I was so excited! A couple of days before the dance... BAM! My arm started to hurt, so I grabbed my heating pad and prescription hydrocodone (finally, something stronger than Tylenol!). This crisis was different; not only was I in pain, but I also had a weird bump on my stomach. A second bump appeared the next day. The doctor told me I had Shingles! Crazy, right? Sadly, I missed the dance.

I got my first taste of adulthood in 2006 when I started the biology program at North Carolina Agricultural and Technical State University in Greensboro, NC (AGGIE PRIDE!). I absolutely loved it. Freshman year was a blast; dance clubs and no parental supervision (WHAT?!). Although attended my fair share of college parties and festivities, I was always cautious enough to stay hydrated, warm, and well rested.

One time there was a cold going around the dorm. Everyone was sick and coughing. Then everyone stopped coughing except for me. My coughing lasted for days and eventually my chest and back started hurting. My dad drove an hour to school and another hour home to take me to Duke University Hospital (my hospital of choice since 1999). The ride to the hospital was excruciating as I could barely sit back in my seat. I had a CT scan and some blood tests and thankfully was not diagnosed with acute chest syndrome (a very common ailment in sickle cell patients). I missed a few days of school, and missing classes in college is tough! When I returned to school, my roommate wanted to know what was going on. This was the first time I had to explain my absence to someone other than my teachers. Luckily my roommate was my best friend from high school so I wasn't as nervous about telling her. I told her I had sickle cell and sometimes my body hurts and I have to go to the hospital. She asked, "Oh ok. So, you're good now?" I replied, "Yep, for now" and we continued as normal. Having sickle cell was always a secret for me. That was big moment for me and I'm glad she was cool enough to not make me feel weird about it.

The summer going into my junior year was interesting. My family had a cookout with aunts, uncles, and cousins. Everyone stayed outside eating and having fun; nothing out of the normal. We all went home and BAM! It felt like that bus hit me again! My back was killing me. I could barely stand. My parents took me to the hospital. I remember sitting in a wheelchair in the lobby, waiting to be called back. A major car accident happened that same day so the hospital was crowded and the wait time was ridiculous. My parents kept asking the when I would be seen. Well, it was taking too long for me, so what did I do? I started screaming and yelling in the waiting room until the staff paid attention. My parents and I were shocked because I am normally pretty quiet. I finally got a room, got some morphine, and was semi-relaxed. I got x-ray and found out that I had pneumonia in both lungs. I got stuck with so many needles and had so many tubes going in me. I remember doctors acting with more urgency than normal. I remember my parents visibly stressed out. That was the first time I had to get a blood transfusion. I did not want one, because I was afraid of catching something from the blood; but most of all, I was afraid because this meant my sickle cell was getting progressively worse. My parents and my best friend begged me to get the transfusion. When the doctors told me that nothing else was working, I finally gave in to the transfusion. Boy that healthy blood did

wonders for me. I felt better instantly. This time however, I was in the hospital for more than two weeks.

Years went by without any hospital stays, but my hip started hurting in 2011. It wasn't a constant pain, so it wasn't yet a big deal. I had been working out more so I figured the pain was due to the increased movement, right? The pain was sharp at times, but it only hurt while walking. However, I started walking with a noticeable limp. I went to an urgent care where they diagnosed me with muscle spasms, prescribed some muscle relaxers, and sent me on my way. The relaxers didn't work so I made a follow up appointment with a sports medicine physician who ordered an x-ray. The doctor told me I had avascular necrosis (AVN) and he wasn't skilled enough to handle it. I never had a doctor tell me they couldn't handle something, so I was immediately on edge. He referred me to a colleague that same day. His colleague confirmed the AVN diagnosis and explained my options: a hip replacement or a core decompression procedure that may or may not help.

The thought of having surgery because of my sickle cell really got me down. My only surgeries until then were wisdom teeth removal and laser treatments for my sickle cell retinopathy (also stressful but nothing like this!). I'd had sickle cell my whole life and not once did any of my doctors tell me that AVN was a common side effect of sickle cell disease. Avascular necrosis is a condition when bone dies as a result of inadequate blood supply; without treatment, it could cause bones to collapse. After discussing my options with my family, we decided on the core decompression. The procedure involves drilling small holes into the dead bone with the hopes of relieving pressure and encouraging blood flow.

The day of the surgery was hard. I remember having a panic attack as they were putting me under and I remember waking up in pain. The whole recovery process was painful, but I'm so thankful to have a good job with good health insurance. I missed 6 weeks of work and was so eager to return. I enjoyed my job and my coworkers, and I didn't want sickle cell to hold me down.

More than a year went by and I thought I was in the clear. However, that familiar sharp pain in my hip returned while walking. I was afraid of going to the doctor because of what he might say. When I finally did go in, he told me that the core decompression did not work and the AVN has progressed. My only option was to get a total hip replacement. I cried in the office. I was 24! Who gets a hip replacement at 24?! The news of a hip replacement was difficult for me to process. I was depressed. The pain evolved into a constant pain. I was on so many pain relievers and anti-inflammatory drugs. The pain was interfering with my job because it was physical and involved lots of walking and lifting. The pain was interfering with my relationships because I was so mad and irritable every day. My limp was so embarrassing and I was running out of excuses to tell people. I finally put my pride aside and decided to get the replacement.

That replacement was the best thing I had ever done! I was walking that same day and went home after only 2 days in the hospital. I had no pain for a few days but I once again, sickle cell wouldn't let me be great. One day I was recovering at my parents' house, watching TV and hanging out with our dog, Shorty, and BAM! The pain I felt in my whole body was the worst pain I have ever felt even to this day. I was home alone again and had just accepted a friend's

offer to come keep me company. When that pain hit I called her back to cancel and tried to get off the phone quickly but she wouldn't let me. She kept asking why, what's wrong, who is with you, etc. I eventually told her that I had sickle cell and it was acting up and I needed to call my parents. She was the third person I told (after my freshman year roommate and a longtime boyfriend). To my surprise she told me her mom has sickle cell and she takes care of her all of the time!

Being the good friend that she is, she came over (even after I uninvited her) and drove me to the hospital. She stayed with me until my mom arrived and waited until I was admitted. The pain with this crisis was so intense. I was in the hospital for two weeks just to get in under control. When the doctors told me I needed a blood transfusion, I did not fight it this time! I still remember that pain. I was later told that my post-surgical care contributed to the intense crisis after the surgery. I was out of work for 2 months.

Fast forward to 2017: I was offered a job I never would have imagined. I was given the opportunity to travel the world as a consultant. Although I was afraid of having a sickle cell episode far from home, I could not turn the job down. My first assignment was in Prague, Czech Republic! I was so afraid but YOLO, right? I went to my hematologist to confirm that it was okay for me to fly for such long a distance, and she gave me the OK! I bought some compression socks, a medical ID bracelet, filled extra pain medicine prescriptions, and flew to the other side of the world. I flew back and forth to Prague for 4 months with no issues!

My second assignment was in INDIA and I was terrified! At least Prague was in Europe with first world hospitals and medical care. My hematologist told me I was okay to make the trip as long as I took the same precautions. She also told me to increase my water intake since India is so hot. I drank so much water while I was there, everyone around me noticed and commented. To my surprise, I did survive! While in India however, my shoulder started hurting. I figured flying and carrying luggage for months was just tough on my body. I flew back and forth to India for 8 months and my shoulder hurt for 6 of them.

When that assignment was over and I was finally able to stay at home for few months, I had my shoulder examined in 2018. I made an appointment with a shoulder specialist and the first thing he said to me was, "Have you heard of avascular necrosis?" My heart dropped. I never expected to have to have a surgery on my shoulder. Depression came back and I was stuck in a pity party for myself, but I didn't wait as long this time. I scheduled my surgery the following month. The recovery for a shoulder replacement is like nothing I have ever experienced. It was painful and annoying, so much harder than the hip replacement. I also had physical therapy. Thankfully, I had a great surgeon who put in a lot of effort to coordinate my pre- and post-op care with my hematologist. Because they worked together, I didn't have the sickle cell related complications that I had with my hip replacement. With the support of my friends and family, I got through it.

It's now February 2020 and my health is pretty good. I haven't had any major crises and no new AVN diagnoses. Although my sickle cell is under control, it is always in the back of my mind. Honestly, I am afraid of the more serious complications like stokes and pulmonary hypertension and think of them quite often. I have daily minor aches, still deal with my retinopathy, and experience fatigue frequently. However, I don't let sickle cell slow me down. I have a full time

job, work out 5x a week, and continue to travel the world with my friends. I put in extra effort to pay attention to my body, ensuring any minor aches and pains do not escalate into something more serious. I have accepted the realization that my sickle cell problems will increase as I age. Nevertheless, I wear my “battle scars” proudly. I am not ashamed or embarrassed to tell people I have sickle cell. When people ask about my noticeable surgical scars, I take it as a learning opportunity. I realize that it’s better for me educate people and bring awareness to sickle cell. I’m always surprised at the number of people, especially black people, that don’t know much about it. But the more people that know about sickle cell, the more people will care, and the more people will donate to funding to support research and treatment for those in the sickle cell community. I look forward to a future where there are more affordable treatment options for sickle cell patients and more resources for their caregivers.

Cheers to many more healthy years!

Lyndsey



February 19, 2020

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,

I am the CEO and Medical Director of the Sickle Cell Disease Association of America, Michigan Chapter. Our statewide organization provides non-medical services to Michigan residents living with sickle cell disease. Our primary mission is to maximize the quality of life of our patients. I am also an attending pediatrician in the Comprehensive Sickle Cell Clinic at Children's Hospital of Michigan where I have provided outpatient care to children with sickle cell disease for over 30 years. I have witnessed first-hand their pain and suffering.

It is well documented in the literature that sickle cell patients have historically faced disparities in access to quality care, particularly in the adult population. In fact, there is a peak in mortality at the time of transition from pediatric to adult care primarily because adult health care providers are not capable of or willing to care for them. We also know that the life expectancy is nearly 30 years shorter than the national average and there is no universal cure for the disease. Sadly, I have attended 3 funerals in the past 2 months.

I am writing to express our concerns regarding the potential negative impact your "Sickle Cell Disease: Draft Evidence Report" could have on the 2,800 individuals living with sickle cell in our state and across the country. It in effect places a dollar value on the quality of life of our patients. While the report places little value on the difference of one day's hospitalization, our organization represents a community of patients who would treasure one less day for each hospital stay – because a year with sickle cell often results in multiple hospitalizations. Medications that can reduce this burden – in cost, job and educational time lost, family disruption, and other life disruptions – would be invaluable.

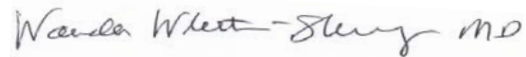
SCD was first described in the United States in 1910. However, the first disease modifying medication did not become available until 1998 with the FDA approval of hydroxyurea. For the next 20 years this was the only available treatment other than supportive care and blood transfusions. The availability of the three new medications – L-Glutamine (Endari), Voxelotor (Oxbryta) and Crizanlizumab (Adakveo) have the potential to improve the quality of life of these patients and offer them new found hope. Multiple promising clinical trials provide the potential for more innovative treatments in the foreseeable future.

The hallmark of SCD is unpredictable, indescribable pain. Approximately 30% of adults living with SCD have pain every day requiring chronic opioid therapy to maintain any semblance of a productive and meaningful life. In spite of this, when patients present to the emergency room they are frequently

perceived as drug seeking. They also experience longer wait times for pain medication than cancer patients. The current opioid crisis has increased the barriers to access much-needed pain medication producing yet another hurdle in our patients' struggle to battle this illness that can have a tremendous negative impact on every aspect of their lives.

On behalf of the thousands of individuals and families we represent, we urge you to consider the broad-ranging immeasurable impact of each healthy day an individual with sickle cell disease is able to add to his or her community. These days add up to far more than the limited life extension your report cites.

Sincerely,

A handwritten signature in black ink that reads "Wanda Whitten-Shurney MD". The signature is written in a cursive style and is positioned above a light blue horizontal line.

Wanda Whitten-Shurney, M.D.
CEO & Medical Director

February 20, 2020
Institute for Clinical and Economic Review
Two Liberty Square
Boston, MA 02109

RE: The Draft Evidence Report for the Treatment of Sickle Cell Disease

Dear Dr. Pearson,

On behalf of the tens of thousands of individuals living with sickle cell disease (SCD) in the United States, we write to provide public comment on the Sickle Cell Disease: Draft Evidence Report. We appreciate ICER bringing attention to SCD and the drastic need for treatment, with great assistance from the sickle cell disease community. We acknowledge and thank the organization for seeking input from patients and patient advocacy organizations, and gathering the patient perspective on this devastating disease. However, given the sparsity of evidence currently available, we recommend for ICER to suspend their review. This will acknowledge the significant shortcomings of the analysis and the need for additional time to ensure adequacy of the report. We encourage your organization to act responsibly and avoid producing a report that may unintentionally introduce, perpetuate or exacerbate inequities. We recommend rescheduling the final report to take place in line with [the timeline proposed by the National Institute for Health and Care Excellence \(NICE\)](#) for review of these sickle cell disease treatments.

Sickle cell disease is a devastating condition robbing people of their lives every single day, a battle that is made worse by stigma and prejudice towards those who are impacted. While racism and discrimination are acknowledged in the report as monumental barriers to care for sickle cell patients, the economic model fails to incorporate these important factors. Without access to real-world data on how these new treatments impact vulnerable populations, your report will inaccurately measure benefit and in turn can result in inequitable denial of access. Equity needs to be more systematically considered by incorporating these complex historical and sociological processes into the base case model. We reiterate our comments from previous letters that ICER is conducting this review without ample long-term or patient experience data. Conversely, simplifying the model without inclusion of these factors will underestimate the magnitude of health and economic burden associated with sickle cell disease.

Pain is a difficult outcome to measure due to its multifaceted and subjective nature. Societal factors and bias influence beliefs, perceptions, and behaviors, all of which have important implications on treatment and care. The way an individual interprets the pain, or learns to cope with its unpredictability, can greatly moderate the way pain affects his or her life. Given these challenges to measure chronic pain, the measurement of acute vaso-occlusive crises (VOCs) are often the focus of clinical trials. These utilize available data in medical records to document patients' encounters with the health system for treatment of pain. However, VOCs are only one of the many complex complications that impact patients' quality and longevity of life. Likewise, patients report that VOCs are sometimes not the most impairing parts of their sickle cell disease, rather other complications like chronic pain, fatigue, and sleep disturbances have greater impacts. Real-world data that capture how these drugs impact not only VOCs but other effects beyond the restrictive design of clinical trials are critical in order to assess the true value of these treatments.

We hope that you consider this recommendation to suspend the review of these sickle cell disease treatments. In doing so, our community would look forward to furthering our collaboration with your organization and partnering to ensure the most accurate real-world data are available prior to finalizing this assessment.

Sincerely,

Axis Advocacy

Cayenne Wellness Center and Children's Foundation

Dreamsickle Kids Foundation, Inc.

Hope for SCD

International Association of Sickle Cell Nurses and Professional Associates

Kids Conquering Sickle Cell Disease, Inc.

The Martin Center Sickle Cell Initiative

Maryland Sickle Cell Disease Association

MTS Sickle Cell Foundation

New York State Sickle Cell Advocacy Network

Ohio Sickle Cell Affected Families Association

A Precious Organization for Sickle Cell

RedMoon Project, Inc.

SCD Forum

Sick Cells

Sickle Cell Association of St. Louis

Sickle Cell Awareness 365

Sickle Cell Community Consortium

Sickle Cell Disease Association of America, Michigan Chapter, Inc

Sickle Cell Disease Association of America Ohio Sickle Cell and Health Association

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 Foundation of Minnesota

Sickle Cell Thalassemia Patient Network

Sickled Not Broken Foundation of Nevada

Supporters of Families with Sickle Cell Disease, Inc.

SWGA Sickle Cell Awareness

Tova Community Healthy, Inc.

Uriel Owen Sickle Cell Disease Association of the Midwest

Individual Community Stakeholders:

Pat Corley, RN, Adult Sickle Cell Disease Nurse

Dr. Lewis Hsu, MD, Pediatric Hematology/Oncology, Chicago, IL

Dr. Charles Otieno, MD, Emergency medicine physician, California

Dr. Ahmar U. Zaidi, MD, Pediatric Hematology/Oncology Physician, Detroit, Michigan



September 20, 2019
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,

Sick Cells is pleased to have the opportunity to engage with the Institute for Clinical and Economic Review (ICER) during their review of treatments for sickle cell disease (SCD). Sick Cells has been heavily involved in this review as a key stakeholder and, because of our high engagement, identified the large constraints of this report. We urge ICER to suspend the review at this time, as this review is premature and inappropriate. The lack of published quality of life and real-world data for these new treatments severely limits ICER's ability to measure the benefit of them. Moreover, the process simply did not allow enough time to adequately and robustly review a disease as complex as sickle cell disease. SCD is too serious and the impact is too large for this vulnerable population to be denied access to therapies because this value assessment was conducted with an inadequate evidence base.

If ICER decides to move forward with the timeline, we have included recommendations for ICER to consider in the final report:

1. Introduction

- a. The authors discuss how patients' baseline health and usual care vary considerably. Thank you for calling this out. Please discuss the implications this has on the analysis included in the report. The comparator is listed as "optimal usual care" however it is not clear how ICER reached a definition of usual care given this variation.
- b. More information is needed in the background section regarding current treatments. Please discuss which patients the medications are recommended for, as the eligibility may be limited. Additionally, provide details regarding the undesirable side effects of each treatment.
- c. Table 1.1 Please provide greater detail on WAC and cost per year.
- d. Include definition for "optimal usual care" utilized as a comparator.
- e. Include identification of data measures and data sources utilized for each outcome. For example, quality of life is listed as an acute outcome, however the quantitative vs. qualitative quality of life improvement is an ongoing tension between the patient perspective and the health economics perspective. Please provide greater detail on the definition and measurements used to capture quality of life as an acute outcome.



- f. Please provide citations for how ICER has defined chronic and acute health conditions.
2. Patient Perspectives
 - a. We acknowledge and thank the organization for seeking input from patients and patient advocacy organizations to gather the patient perspective on this devastating disease. Please provide specifics on how this information contributes to other sections of the report, including the base-case model. It is not clear how this section has impacted the specifics of the report.
 - b. We recommend discussing your methods for capturing the patient perspective. Include citation statements where appropriate. For example, the quotes should be attributed to individuals.
 - c. We appreciate the documentation of racism faced by this community, however, the connection of lack of resources and patient experience to racism is unclear. Please provide citations.
 - d. The “one size fits all” policy for acute pain management is not necessarily a hospital issue. Many states have passed laws on the number of days opioids can be prescribed for acute, opioid naive patients.
 3. Summary of Coverage Policies and Clinical Guidelines
 - a. The authors mention reviewing insurance policies from specific states. It is unclear why these states were selected. The majority of patients with SCD live in other geographic areas not covered by these state-specific insurance policies.
 4. Comparative Clinical Effectiveness
 - a. We appreciate the attention to the limitations of RCT inclusion criteria, including the lack of representation from pediatric populations. Please discuss how this impacts ICER’s ability to accurately measure benefit for the defined population of patients two years of age and older with sickle cell disease.
 - b. In the conclusion section of each treatment, please footnote the data source for quality of life. Please provide details on the measures and methods used to collect quality of life data, noting if any other sources or real-world data was considered.
 5. Long-Term Cost Effectiveness
 - a. We recommend for ICER to develop an equity-sensitive framework for diseases that face increased discrimination and stigma, like sickle cell disease. Anticipated equity effects of this review require adaptation of the usual review processes.
 - b. Quality-adjusted life years fails to capture a wide variety of other benefits such as person’s return to economic productivity, school performance, and ability to function as a caregiver for SCD patients. We recommend using a modified equity-sensitive framework to include these factors in the base case analysis.
 - c. ICER extracted data from Medicare and Commercial claims, however Medicaid is a more common payment source among SCD patients. We recommend utilizing Medicaid data for a more accurate representation of the population.



- d. Prevalence estimates reported by Shah et al. 2019 are based on July 01, 2009 and 31 Dec 2012 data. It is unclear how accurately these prevalence estimates reflect the current period with regards to the acute chest syndrome, stroke, and pulmonary hypertension. Similarly, Van Tuijn et al. 2010 uses dated data to estimate the prevalence. We recommend using updated data sources for these prevalence estimates.
- e. We have identified several concerns related to utility values used in the report:
 - i. Several utility values used in this report are cited from U.K. studies, such as Anie et al., 2012. These utility measurements are inappropriate to be utilized in this assessment, given the differences between health care, health care systems, and the impacts of race and ethnicity in the UK and the US. Complex historical and sociological processes influence the relationships between pain, hospital care, coping responses, and overall quality of life. Given the role of patient utility as a key determinant of value in this model, this is a major concern and limitation. ICER inadequately addresses this uncertainty in the draft report.
 - ii. ICER model input 0.7 utility for uncomplicated SCD patients; however, the Anie utility function is 0.81. Please explain the rationale for using the 0.7 utility function.
 - iii. Anie et al., 2012, estimates “SCD without pain” one week after hospital discharge. These measurements do not accurately reflect the optimal physical, mental, and social functioning associated with SCD patients without pain. Please include utility measures that can more accurately represent the experience of patients without pain.
 - iv. Additionally, Anie et al., 2012, estimates the utility function of patients upon hospital admission from pain crisis. In reality, patients often manage pain in outpatient settings, emergency rooms, or at home. Patients may only be admitted for extreme pain crises. Please include utility measures that can more accurately represent the experience of patients with acute pain crises.
 - v. ICER should assess if utility functions can be derived from the Sick Cells “My Life with Sickle Cell Disease” survey data.
- f. We have identified several concerns related to cost estimates:
 - i. SCD patients experience multidimensional pain, including emotional stress and mood changes. It is unclear if multidimensional pain and the severities of each pain type are accounted for in cost estimates.
 - ii. ICER should review the indirect costs obtained from the Sick Cells survey and consider if the data are appropriate for including in the model.
 - iii. ICER used average cost from Market Scan (non-representative for SCD patients given the use of Medicare and Commercial claims) instead of



individual cost data. Majority of the SCD patients have complicated treatment history and typically have comorbidities; treatment is tailored to each patient. So, without accounting for other factors such as indirect costs, the calculated average treatment cost does not reflect the true patient costs.

- g. ICER should include scenario analysis to assess drug price changes when patent protected drugs expire.
 - h. ICER should consider using Cost Effective Analysis or try using some value of medical innovation beyond QALY. At this moment QALY is missing the value of innovation.
 - i. ICER's scenario analysis shows that discount rate has major impact on patient cost. Changing the discount rate to 1.5% will increase the drug price by more than 20%, meaning the model is considerably impacted by the discount rate change. Provide justification for the discount rate included in this analysis.
 - j. ICER reports "Patients with SCD on optimal usual care are predicted to live to 45 years old, which when discounted at 3% per year equates to approximately 15 additional life-years, 8 additional evLYG, and 8 additional QALYs. " Is this distribution similar in other populations? Please explain in more detail and add relevant citations.
 - k. Table 5.36: The table shows the Medicare population reports higher prevalence of pHTN, HF, and CKD for ages 18-45 as compared to the prevalence of age 46 and over predicted by model. Please explain how the model accounts for these differences.
 - l. Baseline prevalence rate over-reported such as pHTN: The model assumes a high prevalence of organ damage at young age. Please justify the rationale for the high prevalence for organ damage.
 - m. ICER is potentially over estimating mortality. Patients have mortality risk assigned to each comorbidity thus potentially double counts the mortality risk. ICER should consider methods used by Krueger et al. 2013.
6. Potential Other Benefits and Contextual Considerations
- a. ICER mentions the impact of racism and bias but does not say how the model accounts for these factors.
 - b. Are the contextual considerations in section 6.2 reflected in ICER's decisions on effectiveness of the medications? Please discuss the use of the information in this paragraph.
7. Value-Based Price Benchmarks
- a. No comments
8. Potential Budget Impact
- a. No comments



Thank you for your consideration of these suggestions.

Sincerely,
Ashley Valentine, MRes
President and CEO



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February 19, 2020

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,

On behalf of the approximately 1000 Sickle Cell Disease (SCD) patients who are current clients of Supporters of Families with Sickle Cell Disease, Inc. I am writing to express our concerns about the potential negative impact that your Sickle Cell Disease: *Draft Evidence Report* could have on our community.

As you stated repeatedly in your report, SCD is a multi-faceted condition that can cause extreme hardships on patients and their families. We at SFWSCD (Supporters'), bear witness to these hardships daily. We see how SCD's impacts on patients vary dramatically from person to person but that they have multiple periods of severe pain and other complications in common. We see things to varying degrees that individuals and families face, things like a life with uncertain length; lowered educational attainment levels, diminished economic opportunity; periods of depression and hopelessness; and so many other issues that have a negative effect on their quality of life.

The therapies have been the years in the making, and just like other Orphan Drugs, the potential for transformative life is what our community deserves. We are afraid that, after reviewing the report, payors whose only interest is in economics will likely be persuaded to be reluctant to cover these therapies and/or refuse to cover them altogether.

Your report summarizes that crizanlizumab (Adakveo) has the potential to extend life by 2.4 years, that voxelotor (Oxbryta) could extend life by 2.1 years and the L-glutamine (Endari) might extend life by approximately 1 year. We think the answer is that the value is immeasurably higher than any one person or any one scientific analysis can quantify. We believe any improvement in care and each gain in life quality, no matter how incremental they may be, is of significant value to every person and their family impacted by SCD. As a point of reference, I am a parent and a social worker of a child diagnosed with sickle cell disease at 2 months of age. Our family emotional wellbeing has varied from being scared, feeling isolated, exasperated and misunderstood. Living with an expiration date over your loved one's life is extremely difficult, frustrating, and overwhelming. I lost my career when our son was born, and our entire life changed. The sickle cell diagnosis changed the core of our family and how we operate. Currently, our

child requires oxygen daily and suffers from constant hypoxia that is impacting education achievement, which has the long-term impact of affecting his income potential. Until these drugs, I not only wondered, but mulled over, how I would help him navigate his educational journey and what that would look like. I personally, am excited about the new therapies and the many new possibilities that life now can hold for him.

That is why we urge you to more strongly consider the unmeasured costs of SCD before releasing your evidence report in April. At the very least, we urge you to more strongly emphasize the significant, immeasurable value of even small improvements in life expectancy, family system and societal benefit and patient life quality.

Sincerely,

A handwritten signature in black ink, appearing to read 'Velvet Brown Watts', with a long, sweeping horizontal line extending to the right.

Velvet Brown Watts, MSW, CM

Supporters of Families with Sickle Cell Disease, Inc.

President/CEO/Parent

February 17, 2020

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
Two Liberty Square, 9th Floor
Boston, MA 02109

RE: Sickle Cell Disease Draft Evidence Report

Dr. Pearson,

Terumo BCT appreciates the opportunity to provide comments to the Institute for Clinical and Economics Review's (ICER) Sickle Cell Disease (SCD) Draft Evidence Report. Terumo BCT is a global leader in blood component, therapeutic apheresis and cellular technology. We are committed to ensuring patients across the world have access to our products and therapies, importantly SCD patients.

After carefully reviewing ICER's recently released SCD Draft Evidence Report, we feel it important to share our concerns regarding the transfusion data used as a comparator to the novel therapies.

Transfusion is a mainstay in the management of sickle cell disease (SCD) patients and should be considered "optimal usual care". Transfusion modalities, including simple transfusion, manual transfusion and automated red blood cell exchange are different procedures as noted in the recently published American Society of Hematology (ASH) guidelines for transfusion support.^{1,2} As such, each transfusion modality has a unique procedure, required equipment, clinical consideration as an intervention for the treatment of sickle cell disease and its related complications and treatment costs. Patient risk and benefits also differ between the three different transfusion modalities, as described below.

While sickle cell disease (SCD) arises from a single point mutation, there exists tremendous heterogeneity with regards to the multiple genotypes and phenotypes seen from a pathophysiologic perspective as well as heterogenous disease severity and sickle cell-related complications that are seen clinically. Considering that SCD is a systemic disease with the potential to affect numerous organs acutely, chronically, and both (acute-on-chronic), leading to high morbidity and unacceptably high mortality, it is relevant to note that red blood cell transfusion (RBC) is critical in managing acute and chronic complications seen with this disease.^{3,4}

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The common goal of transfusion therapy and exchange transfusion is to maintain patient hemoglobin S levels (HbS%) below a target threshold to reduce SCD-related complications, most notably stroke¹. Additional goals include decreasing blood viscosity and increasing blood flow, increasing oxygen saturation, improving oxygen-delivery capabilities, increasing hemoglobin (Hb), suppressing the production of red blood cells containing HbS.^{7,8}

Simple Transfusion or “top-off” is a transfusion modality whereby healthy red blood cells (RBCs) are transfused without removing any patient blood volume or defective RBCs; a few units of blood are given through an IV drip causing an increase in intravascular volume. While this procedure typically requires the fewest red cell units, hyper viscosity and transfusion-associated circulatory overload (TACO) often occur, along with a faster rate of iron accumulation leading to iron overload necessitating iron chelation therapy.⁶

Exchange transfusion reduces the level of HbS% relative to HbA, thus improving the oxygen carrying capacity of blood and reducing the sickling process seen in SCD patient blood. Exchange transfusions are divided into two categories, as further described below.

Manual Exchange (*partial exchange transfusion/partial manual exchange*) is a transfusion procedure whereby a patient undergoes serial phlebotomy and transfusion, removing patient’s blood followed by the sequential infusion of healthy RBCs. This modality is significantly longer and exposes patients to significant fluid shifts. While this procedure may be suitable for very small patients, achieving a desired final HbS (HbS%) may not be possible and may still lead to iron chelation therapy requirements. Additionally, HbS% is not reduced as quickly or effectively as seen in automated exchange transfusion.⁶

Automated Red Blood Cell Exchange (*RCE, RBCX*) Automated red blood cell exchange is a procedure whereby a patient’s defective RBCs and healthy RBCs are exchanged *simultaneously*, maintaining isovolemia throughout the procedure via the continuous blood removal with saline or red cell replacement, minimizing acute blood volume shifts. This type of transfusion modality takes significantly less time compared to a manual or partial manual exchange, with a longer duration between procedures than either simple or manual transfusions and more rapidly and efficiently maintains targeted hemoglobin S levels.¹¹ Automated exchange is an iron neutral procedure that prevents iron overload and costly iron chelation therapy. Additionally, automated transfusion allows for individualized treatment that allows for not only the effective management of blood utilization per procedure but also precise programming of pre-HbS, post-procedure HbS%, hematocrit, FCR (fraction of cells remaining) and overall fluid balance to optimize each transfusion. An apheresis device, trained HCPs are required for automated exchange.^{9,10} Automated exchange also allows for the optimization of red cell units utilized via red cell depletion with concurrent volume replacement prior to automated exchange as recommended by the recent ASH transfusion guidelines.²

Table 1: The table below illustrates the benefits and potential risks associated with each unique transfusion modality:

	Automated Red Blood Cell Exchange	Manual Exchange	Simple Transfusion
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Isovolemic Procedure	Yes, simultaneous exchange process leads to an isovolemic procedure	No; sequential transfusion leads to patient volume shifts	No; patients' blood is "topped off"
Blood Viscosity	No	No	Yes
Accurately Predict Final HCT%	Yes	No	No
Accurately Predict Final HbS%	Yes	No	No
Procedure Time (minutes)	86-127 ^{10,12-15}	120-245 ^{10,12-14}	180-360 ¹³⁻¹⁵
Days Between Procedures (days)	28-47 ^{10,12}	120-245 ^{10,12-14}	Variable (short interval) ⁶
Manages Iron Overload	Yes*	May require chelation therapy	Typically requires chelation therapy
Specialized Equipment	Apheresis Device	No	No
Specially Trained HCP(s) Required	Yes	No	No

*Chelation therapy may be required if patient already overloaded from previous manual or simple transfusions.

Table 2: As previously noted, three distinct transfusion modalities and a heterogeneous SCD patient population led to recommendations in selecting a transfusion modality in the recently published ASH Guidelines for Transfusion Support:²

	Automated Red Blood Cell Exchange	Manual Exchange	Simple Transfusion
SCD Patients with Severe Acute Chest Syndrome	Recommended	Recommended	Not Recommended
SCD Patients with Moderate ACS	Recommended	Recommended	Recommended
SCD Patients Receiving Chronic Transfusions	Preferred over Simple and Manual Transfusion		
Rapidly Reduce HbS Levels	Preferred over Simple and Manual Transfusion		

For ICER’s research purposes, each transfusion modality has its own CPT® procedure code, simple transfusion (36430), manual red blood cell exchange (36450 - 36456) and automated red blood cell exchange (36512).

Thank you for the opportunity to submit comments. Should you have any questions or if you would like to discuss these comments further, please reach out to **Alicia Silver**, Terumo BCT Manager, Market Access & Health Economics at alicia.silver@terumobct.com or 612-271-8315.

References

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Submitted via e-mail to publiccomments@icer-review.org

Institute for Clinical and Economic Review
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RE: Open Comment on Institute for Clinical and Economic Review *Crizanlizumab, Voxelotor, and L-Glutamine for Sickle-Cell Disease: Effectiveness and Value Draft Evidence Report*

The National Minority Quality Forum is submitting this open comment on the January 23, 2020, Institute for Clinical and Economic Review (ICER) draft evidence report *Crizanlizumab, Voxelotor, and L-Glutamine for Sickle-Cell Disease: Effectiveness and Value* (ICER Draft Report).

The National Minority Quality Forum is a 501(c)(3) not-for-profit, nonpartisan, independent research and education organization. The Forum’s vision is a research, delivery, and financing system that provides quality and effective health services to the biodiverse population of the United States in the 21st century. The Forum contributes to the national dialogue to ensure health policies are grounded in scientific and clinical evidence and that they place a priority on the quality of care and patient outcomes in all populations.

Two new therapies (crizanlizumab and voxelotor) and one relatively new therapy (L-glutamine) have become available for patients with sickle-cell disease (SCD). ICER undertook an assessment to evaluate “the clinical effectiveness and cost effectiveness of crizanlizumab, voxelotor, and pharmaceutical-grade L-glutamine for patients with SCD.”¹ Although ICER recognized that each of these drugs has novel clinical effectiveness that could reduce pain and suffering and improve quality of life for SCD patients, it did not find that any of them to be a high-value medication according to its cost-effectiveness criteria.² This failure to meet ICER’s criteria for high value has little to do with the drugs value to SCD patients. From the perspective of patients and their physicians and caregivers, ICER’s value metrics introduce questionable benchmarks that distort the definition of high medical value as it is commonly understand.

We have reviewed the ICER Draft Report and considered the consequences that our comments might have. ICER—a nongovernmental agency—certainly has a right to its opinion. ICER and the Forum work from profoundly different principles about the obligations of medicine and how those obligations inform patient care.

The Forum’s values are predicated on two axioms: (1) Every patient should have access to appropriate care, and (2) health systems and their treatment protocols should not elevate a patient’s risk for a poor outcome or a poor quality of life. Summarized: Do no harm. Based on these predicates, we view treatment plans, policies, assessments, or value judgements that deny

¹ Pamela Bradt, Eldon Spackman, Patricia Synott, Rick Chapman, David M. Rind, and Steven D. Pearson, *Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value*, Institute for Clinical and Economic Review, January 23, 2020, <https://icer-review.org/material/sickle-cell-disease-draft-evidence-report/>, p. 11.

² Bradt et al., *Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease*, p. 92.

access to appropriate care as social determinants of health, and we see their negative consequences as reportable events.

ICER operates from a different frame of reference. Fundamental to every one of ICER's assessments is the application of its benchmark cost thresholds to help it distinguish high-value from low-value care. A medication that is inferior in its medical benefit, but whose cost meets ICER's long-term money value and short-term affordability valuation could be designated high value compared with a more clinically effective, but more costly, medication. A more costly, but clinically effective, medication could be rated as low value in the ICER assessment. ICER conveniently ignores that clinical effectiveness and lowering of patient risk are inextricably linked, and cost does not mediate that relationship.

ICER is an advocate for health-care systems that regard structural inequalities as acceptable by-products of value assessments that promote the elevation of a patient's risk for a poor outcome or a poor quality of life in order to avoid exceeding cost thresholds. Working from its financial model, ICER withholds a high-value assessment for any of the three novel SCD treatments because the cost exceeds ICER's predetermined cost thresholds, providing dubious justification for health systems to limit or deny access to these medications. The Draft Report does not suggest that the withholding agency seek a patient's consent to this care limitation or suggest the appropriateness of reporting the negative consequences of the policy.

The Forum sees no useful purpose in trying to deconstruct the ICER value assessment to show that flaws, inconsistencies, and inequities disqualify the Draft Report as a useful assessment of the value of these new treatments for SCD. Actually, ICER's assessment model succeeds at what it is designed to accomplish: to determine whether any of the medications meets its narrow definition of high value by having a market price that does not exceed its benchmark cost threshold.

We disagree with the premise that medical value must be a function of cost. The corollary of that premise is a tiered health-care system where patient risk is deliberately elevated and inequities are commonplace. The US Food and Drug Administration by its approval and ICER by its own evaluation have determined that the three SCD medications are clinically effective. Our root-and-branch rejection of the ICER Draft Report is founded on the operational assumptions that are the report's underpinning. They are antithetical to our value, fundamental to medicine, which we summarize as *do no harm*.

ICER and the Forum have different opinions, based on different values; we believe that our values more closely align with what any SCD patient (or any patient, for that matter) would expect of the health-care system. Providers that build their SCD-treatment plans on the ICER Draft Report without informing patients of its inherent limitations not only will violate a trust relationship but also will introduce inequalities and poor health outcomes into their systems while diminishing the quality of life for those who come to them for care.

To the Institute of Clinical and Economic Review,

I was tested at birth and then diagnosed with Sickle Cell Anemia Hemoglobin SS at three weeks of age. I am a passionate advocate for the sickle cell community. Initially, when I heard about the ICER review, I was saddened and offended. I felt as though our community was being told we didn't deserve the new costly medications because they are expensive. I am terrified that this review will deter insurance companies and make other pharmaceutical companies reluctant to come up with new treatments. I know that if patients have access to treatments that decrease hospitalizations, overtime money will be saved.

I am appreciative of this opportunity to educate and give you a better understanding of my community and the realities of living with sickle cell.

BY the time I was 16, I already had bilateral hip replacements, several hospitalizations, and gone through acute liver failure. I have always had big dreams and ambition. After I graduated high school, I was fully prepared to go off to college. That desire had to be placed on hold because my body was constantly failing me. I became so desperate that I had a bone marrow transplant. I felt as though the constant pain, operations, silent strokes, and acute chest syndrome bouts, were keeping me from being able to reach my full potential. After going through chemotherapy and radiation, I received my transplant. My mother was my half-matched donor. Unfortunately, I rejected and still have sickle cell.

As a result of the transplant, It took me years to recover as my bone marrow shutdown. The new medications mean the world to me because, I have exhausted all other options. I am not a candidate for gene therapy because I had a bone marrow transplant. I have been on Hydroxyurea for years. I started it mainly because I was getting acute chest syndrome every year. For almost eight years I have not had acute chest. However, last year I had it three times. My doctor and I both feel that Hydroxyurea is losing some of its effectiveness. I can't receive exchange or simple blood transfusions because I have developed over 20 antibodies. My last transfusion was what sent me into liver failure. I am at peace with not being cured of sickle cell and have been waiting for new treatments to help me live a better quality of life.

If you don't have sickle cell or care for someone with it, it is impossible to understand what we deal with on a regular basis. My two biggest challenges right now are chronic pain and fatigue. I can usually push through the pain, because I have developed a high pain tolerance. However, the fatigue is what knocks me down.

There is a misconception that sickle cell patients are lazy drug seekers. That is so far from the truth. I am in school pursuing a degree in clinical psychology. I am connected to a lot of sickle cell warriors and every single one of them is working hard to accomplish their goals. We are doing more than just living with sickle cell, we are thriving with sickle cell.

I have come up close and personal with stigma. I have been told by doctors and nurses that I can't possibly be in pain because I look too good. I have had a doctor refuse to treat me and suffered in pain until a new doctor came in. When I had my transplant, I was on the oncology

floor of the hospital. At the time, I felt as if I was receiving celebrity treatment. Looking back, the treatment I received then is what all sickle cell patients deserve. I remember the nurses running in with IV Benadryl to treat the nausea from chemotherapy before I could even ask for it. They would ask me if I wanted it pushed fast or slow. A week after I rejected the transplant and was officially diagnosed with sickle cell again, I had a crisis. I went to the same hospital that had been treating me with the IV Benadryl and was told “we don’t give IV Benadryl to sicklers because you guys like the rush too much”. The Sickle Cell community has always felt that there was a huge difference in the way we were treated in comparison to how cancer patients are treated. During the transplant process, I saw that firsthand.

There is more to sickle cell than just physical complications. Nobody seems to address the emotional and mental toll that sickle cell can have. The pain and fatigue for many leads to isolation and depression. The sickle cell community is very close knit. We form close bonds and connections with each other. Over the last two years, I have lost track of the number of friends I have lost to this disease. Last year I started antidepressants because I was in a constant state of grief. I am 28 years old and thought that I would have a master’s degree by now. I see my friends moving on with life and sometimes get sad that I haven’t been able to keep up.

Another issue that isn’t often talked about is the out of pocket cost. Sometimes, insurance doesn’t cover everything. We have co-pays for appointments and prescriptions. Even little things like parking fees add up. Last week, I had five different appointments and probably spent at least 100 dollars just to park my car.

I hope that sharing my story and perspectives, helps you during the review process. Often, decisions are made for this community without us. I greatly appreciate your time and consideration.

Teonna Woolford