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Systematic Literature Review

Health State Utilities for Sickle Cell Disease: A Catalog Prepared From a Systematic Review

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ABSTRACT

Objectives: Sickle cell disease (SCD) is a complex, chronic condition that impairs health-related quality of life of affected individuals and their caregivers. As curative therapies emerge, comprehensive cost-effectiveness models will inform their value. These models will require descriptions of health states and their corresponding utility values that accurately reflect health-related quality of life over the disease trajectory. The objectives of this systematic review were to develop a catalog of health state utility (HSU) values for SCD, identify research gaps, and provide future directions for preference elicitation.

Methods: Records were identified through searches of PubMed and Embase, Tufts Medical Center Cost-Effectiveness Analysis Registry, reference lists of relevant articles, and consultation with SCD experts (2008-2020). We removed duplicate records and excluded ineligible studies. For included studies, we summarized the study characteristics, methods used for eliciting HSUs, and HSU values.

Results: Five studies empirically elicited utilities using indirect methods (EQ-5D) (n = 3) and Short Form-6 Dimension (n = 2); these represent health states associated with general SCD (n = 1), SCD complications (n = 2), and SCD treatments (n = 3). Additionally, we extracted HSUs from 7 quality-adjusted life-years-based outcome research studies. The HSU among patients with general SCD without specifying complications ranged from 0.64 to 0.887. Only 36% of the HSUs used in the quality-adjusted life-year-based outcomes research studies were derived from individuals with SCD. No study estimated HSUs in caregivers.

Conclusions: There is a dearth of literature of HSUs for use in SCD models. Future empirical studies should elicit a comprehensive set of HSUs from individuals with SCD and their caregivers.

Keywords: cost-effectiveness analysis, health state utility, sickle cell disease, systematic review.

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Introduction

Sickle cell disease (SCD) is a group of genetically inherited disorders of hemoglobin affecting more than 20 million people worldwide.[1] In the United States, approximately 100 000 people live with SCD; most are of African descent.[1] SCD can lead to a number of acute and chronic complications including acute pain episodes, stroke, acute chest syndrome, chronic pain, symptomatic anemia, and an increased risk of infections and organ damage, each associated with significantly increased economic burden.[1,2] Recent advances in medical care have resulted in a major reduction in SCD-related childhood mortality; SCD has evolved from being a life-threatening disease of childhood to a chronic disease in adults.[3]

Despite achievements in mortality reduction, the substantial impact on health-related quality of life (HRQoL) of these individuals and their caregivers warrants attention. Previous studies have demonstrated the significant relationship between experiencing SCD complications and deterioration in HRQoL among both children and adults.[4] Vaso-occlusive crisis is a typical example, which can cause pain and impair functioning and well-being.[5] Furthermore, treatment-related complications such as iron overload and the need for chelation with transfusions and graft-versus-host disease (GVHD) with allogeneic hematopoietic stem cell transplantation (alloHSCT) can significantly impair HRQoL.[6]

HRQoL is best captured by defining the relevant health states, eliciting values that represent the utility of each of these states, and then multiplying each of these by the time spent in each health state to estimate quality-adjusted life-years (QALYs). Health state utility (HSU) values can be elicited directly through empirical data collection or indirectly through administration of survey instruments that exist for this purpose. The 4 direct elicitation methods are visual analog scale (VAS), time trade-off, standard gamble, and discrete choice experiment.[7] The surveys most often used when using the indirect method are the dEQ-5D, Short Form-6 Dimension (SF-6D), or the Health Utilities Index.[8] The

development of these instruments is grounded in the multi-attribute utility theory.[8]

HSUs are also used to estimate QALYs gained by a new intervention over the standard of care in cost-effectiveness analysis (CEA). Estimating the value of emerging therapies using CEAs will be particularly important in SCD as genetic therapies are pursued, because these may prove curative for patients with SCD. Indeed, the Cure Sickle Cell Initiative funded by the National Heart, Lung, and Blood Institute (curesickle.org)[9] is a large collaborative research effort intended to accelerate the development of genetic therapies to cure SCD. Nevertheless, high up-front costs are associated with genetic therapies.[10] An existing genetic therapy for β-thalassemia, another hemoglobin disorder, costs approximately $1.8 million per treatment.[11] Nevertheless, the expense of 1-time administration may be offset by the alternative of repeated administration of standard therapies that accumulate large expenses over the lifetime.[12] CEA methods will be useful in valuing the impact of potentially curative therapies on the complexities of SCD experienced over a patient's lifetime.

As members of the National Heart, Lung, and Blood Institute Cure Sickle Cell Initiative, to inform the future QALY-based CEA models, we conducted a systematic review of the published literature and created a catalog of HSUs for SCD-specific comorbidities and treatment complications. In particular, we summarize the main characteristics, designs, and results of studies that estimate HSUs for the SCD population. We identify current research gaps and close them by providing directions for future HSU research for SCD.

Methods

Search Methods and Sources

We conducted a systematic review following the methods of the Cochrane Collaboration and the Agency for Healthcare Research and Quality guidance for systematic reviews and adopted the population, intervention, comparator, outcomes, timing and setting/study design (PICOTS) framework to establish eligibility criteria.[13,14] The adopted PICOTS framework reflects deliberations and decisions made over a 3-month period in late 2019 by an expert panel that included a molecular biologist, clinicians who care for patients with SCD, health economists, evidence synthesis scientists, and librarians (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.08.002). These same investigators decided on the search terms. We searched the PubMed, Embase, and the Tufts Medical Center CEA Registry databases using a prespecified protocol (search terms are displayed in Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.08.002). We also identified articles through screening the reference lists of relevant systematic reviews and consultation with experts.

The framework was executed as a search strategy in PubMed and Embase by the health sciences librarians. The Tufts Medical Center CEA Registry was searched by a health economist. Duplicates were removed and returned studies were screened for eligibility. For studies that met the inclusion criteria, relevant data were extracted and synthesized. The content of this report aligns

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of studies included in this systematic review and reasons for exclusion.

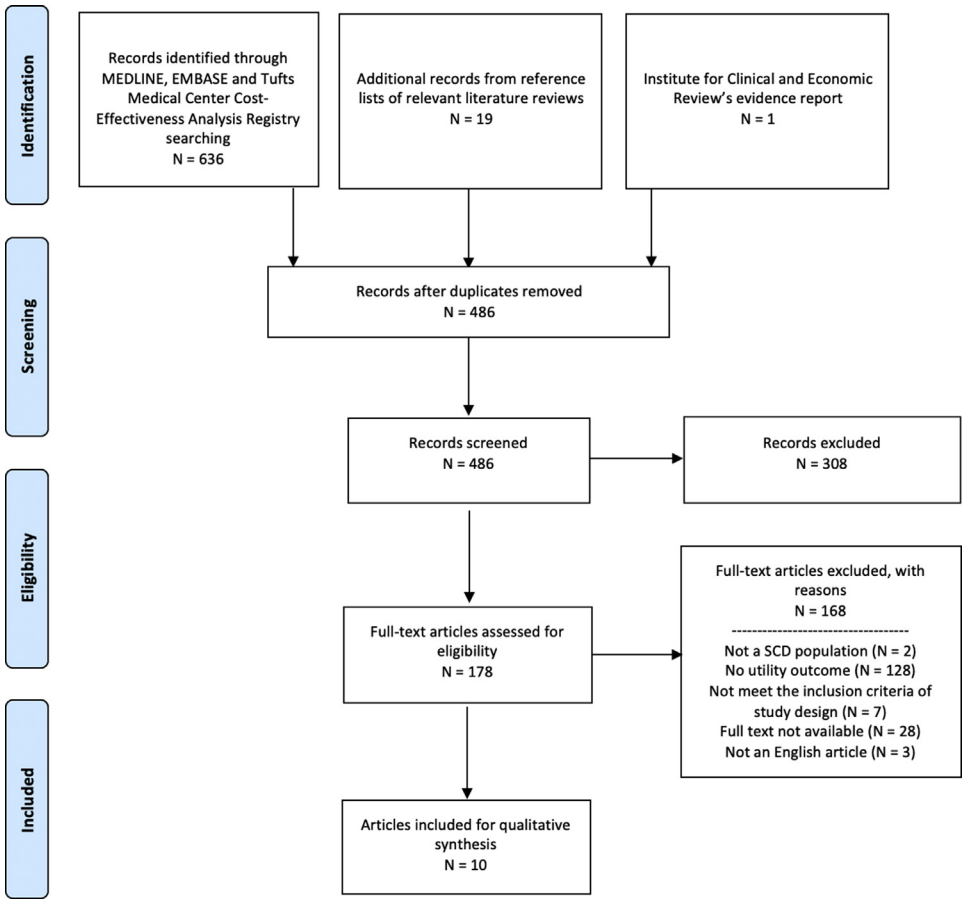

Table 1. Main characteristics of included studies.

Author, year	Study category	Publication type	Study design	Region
Anie et al[18]	Empirical HSU study	Journal article	Retrospective cohort	UK
Arnold et al[19]	Empirical HSU study	Journal article	Retrospective cohort	USA
Ojelabi et al[20]	Empirical HSU study	Journal article	Cross-sectional study	Nigeria
Payne et al[21]	Empirical HSU study	Journal article	Retrospective cohort	UK
Spackman et al[22]	Empirical HSU study	Journal article	Randomized control trial	UK
Arnold et al[19]	QALY-based outcomes research study	Journal article	Cost-effectiveness analysis	USA
Bradt et al[23]	QALY-based outcomes research study	White paper	Cost-effectiveness analysis	USA
Cherry et al[24]	QALY-based outcomes research study	Journal article	Cost-effectiveness analysis	UK
McLeod et al[25]	QALY-based outcomes research study	Journal article	Cost-effectiveness analysis	UK
Spackman et al[22]	QALY-based outcomes research study	Journal article	Cost-effectiveness analysis	UK
O'Brien and Hankins[26]	QALY-based outcomes research study	Journal article	Comparative effectiveness study	No specific country
Lubeck et al[27]	QALY-based outcomes research study	Journal article	Simulated cohort modeling study	USA

with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement for reporting of systematic reviews.[15]

Eligibility Criteria

We included English language full-text articles published in peer-reviewed journals from January 2008 to September 2020. We also searched for full-text white papers and limited our search to the time frame of January 2018 to September 2020, reasoning that information provided in the older white papers would not reflect the current research findings. We excluded conference proceedings when full text was not available for assessment and quality rating. We defined and placed studies into 2 categories. We defined empirically based studies as those that used the direct elicitation methods (VAS, time trade-off, standard gamble, or discrete choice experiment) or the indirect methods of multiattribute utility instruments (eg, EQ-5D, SF-6D). We defined QALY-based outcomes research studies as those wherein QALYs were reported; from which we were called to isolate the HSUs that were incorporated. We excluded studies in which the study population was individuals with sickle cell trait. All types of interventions for patients with SCD, in any geographic setting globally, were eligible.

Study Selection

Records identified through the databases, found from reference lists of relevant systematic reviews, and in consultation with experts were merged. After duplicate records were removed, one reviewer (B.J.) independently screened the titles and abstracts of all references, excluded those based on the predefined criteria, and assessed the full texts of all remaining articles for eligibility. The second reviewer (D.Q.) reviewed 10% of randomly selected references. Discrepancies between reviewers' judgments were discussed and resolved through consensus.

Data Extraction

For the empirical HSU studies, one reviewer (B.J.) extracted the main characteristics and study designs (publication type, study population, region, study design, sample size, instruments used to elicit HSUs) and HSU estimates and uncertainties. For the QALY-based outcomes studies, one reviewer (B.J.) extracted the main characteristics and designs, HSU used, and sources of the HSUs. For the HSUs that were sourced from other published studies, we also extracted the main characteristics of the source studies and instruments used. Sometimes the original HSU values in the source studies differed from those finally included in the outcomes research studies—the authors of the outcome research studies might adjust the original values to better fit their studies. We attempted to replicate and then describe the adjustment method, when possible. The second reviewer verified the extracted data.

Critical Appraisal

We performed a quality assessment for the empirical HSU studies using methods developed by Ara et al[16] and Brazier et al[17] in 2017 and 2019. These domains are measurement of variability, response rates to the instrument used, loss to follow-up, and

Table 1. Continued

Population	Sample size	Instrument/method	Intervention type
Adults with SCD admitted to hospital daycare or inpatient units	510	EQ-5D	NA
Patients with SCD	Intervention group: 26 Control group: 48	EQ-5D	alloHSCT
Adults with SCD	200	SF-6D	NA
Patients with β-thalassemia, SCD, and myelodysplastic syndromes receiving ICT	60	SF-6D	Intervention for SCD complication
Patients with SCD undergoing elective surgery	Intervention group: 18 Control group: 17	EQ-5D	Blood transfusion
Patients with SCD	NA	Based on literature	alloHSCT
Patients with SCD	NA	Based on literature Assumed by the authors	Pharmaceuticals
Patients with SCD	NA	Based on literature Assumed by the authors	Blood transfusion
Patients with β-thalassemia major or SCD undergoing frequent blood transfusion	NA	Based on literature Assumed by the authors	Intervention for SCD complication
Patients with SCD undergoing elective surgery	NA	Based on their own study Assumed by the authors	Blood transfusion
Children with SCD	NA	Based on literature Clinician opinion	alloHSCT Blood transfusion Pharmaceuticals
Patients with SCD	NA	Based on literature	NA

alloHSCT indicates allogeneic hematopoietic cell transplantation; HSU, health state utility; ICT, iron chelation therapy; NA, not applicable; QALY, quality-adjusted life-year; SCD, sickle cell disease; SF-6D, Short Form-6 Dimension; UK, United Kingdom; USA, United States.

handling of missing data.[16,17] For the QALY-based outcome research studies, we assessed the relevance of the target population in the source studies,[16,17] that is, whether the HSUs were derived from studies of individuals with SCD.

Results

Study Selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection and reasons for exclusion is presented in Figure 1. Our search identified 636 references. A total of 19 additional studies were identified from the reference lists of the literature review, and one was identified in consultation with experts. After removing duplicate articles, we screened the titles and abstracts of the remaining 486 references and included 178 references for full-text assessment. Notably, 10 articles met our final inclusion criteria. The schematic diagram in Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.08.002 shows how these articles were categorized—there were 5 empirical HSU studies[18-22] and 7 QALY-based outcomes research studies.[19,22-27]. Two articles (Arnold et al[19] and Spackman et al[22]) contained not only an empirical HSU study but also a QALY-based cost-utility analysis.

Overview of Included Studies

The main characteristics of included studies can be found in Table 1. Of the 5 empirical HSU studies, 1 was conducted in United States,[19] 3 in United Kingdom,[21,22,24] and 1 in Nigeria.[20] A total of 3 were retrospective cohort studies,[18,19,21] 1 was a cross-sectional study,[20] and 1 was a randomized control trial (RCT).[22] A total of 3 studies used the EQ-5D[18,19,22] and 2 studies used SF-6D to elicit HSUs.[20,21] No study used direct elicitation methods.

Five of the QALY-based outcome research studies were CEAs; 2 of the CEAs were set in the United States,[19,23] and 3 were in the United Kingdom.[22,24,25] Moreover, 2 focused on blood transfusion,[22,24] 1 focused on alloHSCT,[19] 1 focused on pharmaceuticals,[23] and 1 focused on interventions for SCD treatment complications.[25] We also found 1 study that compared the effectiveness of SCD interventions that did not specify the region[26] and 1 simulation modeling study that projected outcomes for United States-based cohorts with and without SCD.[27]

The resulting catalog of HSUs comprised 3 categories: HSUs for SCD without specifying complications (general SCD) (Table 2), HSUs for specific SCD complications (Table 3), and HSUs tied to SCD treatments (Table 4). The main characteristics of source studies for the HSUs used in the QALY-based outcome research studies are presented in Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.08.002.

General SCD

One empirical HSU study[20] and 3 QALY-based outcomes research studies reported HSUs for the general SCD without specifying complications.[23,24,27] Utilities range from 0.64 (general female patients) to 0.887 (patients without pain). The empirical study provided HSUs stratified by sex and utility decrements associated with each 1-year increase in age.[20] The 3 outcome research studies include HSUs for patients without

complications,[23] for patients with transcranial Doppler velocity of <200 cm/s,[24] and for patients without pain and patients on average,[27] respectively. Notably, 2 of the outcome research studies calculated the HSUs based on the algorithm from study of Anie et al[18] that mapped the VAS pain scores to utilities.[23,27] Only one of the outcome research studies included HSUs separately for adults and for children and adolescents.[27]

SCD Complications

Pain

Two empirical HSU studies[18,20] and 3 QALY-based outcome research studies[23,24,27] reported HSUs associated with pain. The mean HSU ranged from 0.27 (severe pain) to 0.75 (1 week after discharging from hospital). One empirical study assessed HSUs in patients at admission for acute pain, at discharge, and at 1-week follow-up.[24] The other empirical study estimated a utility decrement for an increase in frequency of pain.[20]

Of the 3 QALY-based outcomes research studies, one applied the same utility values from the first empirical study,[23] one included a utility decrement for pain crises without specifying severity,[24] and the third used the aforementioned mapping algorithm from Anie et al[18] and calculated HSUs associated with minor, moderate, and severe pain for adults and for children and adolescents, respectively.[27]

Stroke

Two QALY-based outcomes research studies included HSUs associated with stroke.[23,24] The utility decrement ranged from 0.162 (minor stroke) to 0.565 (major stroke). Both studies included utilities for different severity levels. One study specified HSUs for minor and major stroke,[23] and the other reported utilities for mild, moderate, and severe states after stroke.[24] We also found a second outcome research study that used a utility decrement for pre-stroke patients with transcranial Doppler scan of >200 cm/s.[24]

Cardiovascular conditions

One QALY-based outcome research study included utility decrements for pulmonary hypertension and for myocardial infarction and heart failure.[23]

Acute chest syndrome

Two QALY-based outcomes research studies provided utility decrements for acute chest syndrome.[23,24] The utility values ranged from 0.06 (over 3 months) to 0.13.

Kidney conditions

One QALY-based outcomes research study provided reported a utility decrement of 0.14 for nephropathy, acute kidney injury, or renal infarction.[23]

Mental health conditions

One empirical HSU study[20] and 1 QALY-based outcomes research study[23] provided HSUs for mental health conditions. The empirical study estimated utility decrements for anxiety and depression.[20] The outcomes research study included a utility decrement because of neurocognitive impairment.[23]

Other complications

One empirical study reported a utility decrement for an increase in the number of any comorbidities.[20] We also found 1 QALY-based outcome research study that included utility decrements because of fatigue and opioid tolerance/dependence[23] and

Table 2. HSUs associated with general SCD.

Author, year	Study population, region	Instrument/method	Health states	Utility values
Empirical HSU study				
Ojelabi et al[20]	Adults with SCD, Nigeria	SF-6D	SCD in general	Utility for SCD in general: 0.65 (SD 0.12) Utility for SCD in general for males: 0.66 (SD 0.11) Utility for SCD in general for females: 0.64 (SD 0.12) Utility decrement because of one year older: 0.023 (SE 0.014)
QALY-based cost-effectiveness analysis				
Bradt et al[23]	Patients with SCD, USA	Based on the algorithm reported by Anie et al,[18] which mapped VAS pain score to utility	SCD without complication	Utility for SCD without complication: 0.80
Cherry et al[24]	Patients with SCD, UK	Based on literature	SCD with normal TCD velocity	Utility for SCD with blood velocity of <200 cm/s: 0.22 (per 3 months)
QALY-based simulation modeling study				
Lubeck et al[27]	Patients with SCD, USA	Based on the algorithm reported by Anie et al,[18] which mapped VAS pain score to utility	SCD in general	Utility for SCD with no pain: 0.887 Utility for adult with SCD in general: 0.695 Utility for children or adolescents with SCD in general: 0.692

HSU indicates health state utility; QALY, quality-adjusted life-year; SCD, sickle cell disease; SE, standard error; SF-6D, Short Form-6 Dimension; TCD, transcranial Doppler; UK, United Kingdom; USA, United States; VAS, visual analog scale.

Table 3. HSUs associated with complications of SCD.

Author, year	Population, region	Instrument/method	Health states	Utility values
Pain: empirical HSU study				
Anie et al[18]	Adults with SCD admitted to hospital daycare or inpatient units, UK	EQ-5D	Pain	Utility at admission for acute pain: 0.39 (SD 0.40) Utility at discharge: 0.65 (SD 0.29) Utility at 1-week follow-up: 0.75 (SD 0.26)
Ojelabi et al[20]	Adults with SCD, Nigeria	SF-6D	Pain	Utility decrement for an increase in frequency of pain: 0.027 (SD 0.007)
Pain: QALY-based cost-effectiveness analysis				
Bradt et al[23]	Patients with SCD, USA	Based on literature	Pain	Utility decrement for acute pain crisis (admission): 0.36 Utility decrement for acute pain crisis (discharge): 0.1 Utility decrement for 2-week pain crisis: 0.23
Cherry et al[24]	Patients with SCD, UK	Assumed by the authors	Pain	Utility decrement for pain crisis: 0.02 (per 3-month)
Pain: QALY-based simulation modeling study				
Lubeck et al[27]	Patients with SCD, USA	Based on the algorithm reported by Anie et al,[18] which mapped VAS pain score to utility	Pain	Utility for adults with severe pain: 0.437 Utility for adults with moderate pain: 0.492 Utility for adults with mild pain: 0.557 Utility for children or adolescents with severe pain: 0.270 Utility for children or adolescents with moderate pain: 0.474 Utility for children or adolescents with mild pain: 0.703
Stroke: QALY-based cost-effectiveness analysis				
Bradt et al[23]	Patients with SCD, USA	Based on literature	Stroke	Utility decrement for minor stroke: 0.16 Utility decrement for major stroke: 0.57 Utility decrement for poststroke on average: 0.30
Cherry et al[24]	Patients with SCD, UK	Assumed by the authors	Stroke	Utility decrement for mild state post first/second/third stroke: 0.03 (per 3-month) Utility decrement for moderate state post first/second/third stroke: 0.08 (per 3-month) Utility decrement for severe state post first/second/third stroke: 0.13 (per 3-month)
			TCD >200 cm/s	Utility decrement: 0.03

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Table 3. Continued

Author, year	Population, region	Instrument/method	Health states	Utility values
Cardiovascular conditions: QALY-based cost-effectiveness analysis				
Bradt et al[23]	Patients with SCD, USA	Assumed by the authors	Pulmonary hypertension	Utility decrement: 0.12
		Based on literature	Myocardial infarction	Utility decrement for myocardial infarction: 0.13
		Based on literature	Heart failure	Utility decrement for heart failure: 0.12
Acute chest syndrome: QALY-based cost-effectiveness analysis				
Bradt et al[23]	Patients with SCD, USA	Based on literature	Acute chest syndrome	Utility decrement for acute chest syndrome: 0.13
Cherry et al[24]	Patients with SCD, UK	Assumed by the authors	Acute chest syndrome	Utility decrement for acute chest syndrome: 0.06 (per 3-month)
Kidney conditions: QALY-based cost-effectiveness analysis				
Bradt et al[23]	Patients with SCD, USA	Based on literature	AKI/Renal infarction	Utility decrement for AKI/renal infarction: 0.14
	Patients with SCD, USA	Based on literature	Nephropathy/CKD	Utility decrement for nephropathy/CKD: 0.14
Mental health conditions: empirical HSU study				
Ojelabi et al[20]	Adults with SCD, Nigeria	SF-6D	Anxiety	Utility decrement for anxiety: 0.029 (SD 0.014)
			Depression	Utility decrement for depression: 0.037 (SD 0.014)
Mental health conditions: QALY-based cost-effectiveness analysis				
Bradt et al[23]	Patients with SCD, USA	Based on literature	Neurocognitive impairment	Utility decrement for neurocognitive impairment: 0.05
Other complications: empirical HSU study				
Ojelabi et al[20]	Adults with SCD, Nigeria	SF-6D	General complications	Utility decrement for an increase in number of complications: 0.05 (SD: 0.013)
Other complications: QALY-based cost-effectiveness analysis				
Bradt et al[23]	Patients with SCD, USA	Based on literature	Opioid tolerance/ dependence	Utility decrement for opioid tolerance/ dependence: 0.07
		Based on literature	Fatigue	Utility decrement for fatigue: 0.12
Other complications: QALY-based comparative effectiveness study				
O'Brien and Hankins[26]	Children with SCD No specific country	Clinician opinion Based on literature	VOC	Utility for patients with severe SCD because of recurrent VOC receiving no treatment: 0.70 (range 0.50-0.90)

AKI indicates acute kidney injury; CKD, chronic kidney disease; HSU, health state utility; QALY, quality-adjusted life-year; SCD, sickle cell disease; SF-6D, Short Form-6 Dimension; TCD, transcranial Doppler; UK, United Kingdom; USA, United States; VAS, visual analog scale; VOC, vaso-occlusive crisis.

another study that used an HSU for patients with severe SCD because of recurrent vaso-occlusive crisis.[26]

SCD Treatments and Treatment Complications

AlloHSCT

One empirical HSU study[19] and 2 QALY-based outcomes research studies[19,26] reported HSUs for patients who received alloHSCT; these ranged from 0.55 (post-alloHSCT patients with graft failure) to 0.95 (post-alloHSCT patients without graft failure). The empirical study assessed HSUs at a mean of 6 years after alloHSCT.[19] One of the outcomes-based research studies included HSUs over the first post-alloHSCT year,[19] and the other included HSUs for patients with and without graft failure or with chronic GVHD over the 5-year post-alloHSCT period.[26]

Table 4. HSUs associated with treatments for SCD.

Author, year	Population, region	Instrument/method	Treatment	Utility values
alloHSCT: empirical HSU study				
Arnold et al[19]	Patients with SCD, USA	EQ-5D	alloHSCT	Utility for post-alloHSCT patients (6 y post-alloHSCT): 0.87 Utility for patients with documented HLA typing or alloHSCT consultation (or with both) but without alloHSCT: 0.91
alloHSCT: QALY-based cost-effectiveness analysis				
Arnold et al[19]	Patients with SCD, USA	Based on literature	alloHSCT	Utility at days +45 post-alloHSCT: 0.71 Utility at days +90 post-alloHSCT: 0.75 Utility at days +180 post-alloHSCT: 0.79 Utility at days +365 post-alloHSCT: 0.84
alloHSCT: QALY-based comparative effectiveness study				
O'Brien and Hankins[26]	Children with SCD No specific country	Clinician opinion Based on literature	alloHSCT	Utility for post-alloHSCT patients with graft failure: 0.55 (range 0.35-0.75) Utility for post-alloHSCT patient with chronic GVHD and with no graft failure: 0.65 (range 0.45-0.85) Utility for post-alloHSCT patient with no graft failure and no chronic GVHD: 0.95 (range 0.75-1.0)
Blood transfusion: empirical HSU study				
Payne et al[21]	Patients with β-thalassemia, SCD, and myelodysplastic syndromes receiving ICT, UK	SF-6D	Chronic blood transfusion ICT	Utility: 0.66 (range 0.37-0.95)
Spackman et al[22]	Patients with SCD undergoing elective surgery, UK	EQ-5D	Preoperative transfusion	Utility for patients who received no preoperative transfusion At baseline: 0.793 (SD 0.298) At follow-up: 0.864 (SD 0.190) Utility for patients who received preoperative transfusion At baseline: 0.760 (SD 0.236) At follow-up: 0.854 (SD 0.166)
Blood transfusion: QALY-based cost-effectiveness analysis				
Cherry et al[24]	Patients with SCD, UK	Assumed by the authors	Chronic transfusion ICT	Utility decrement for prestroke patients on simple, exchange or combined transfusion: 0.02 (per 3 months) Utility decrement for patients on injection chelation: 0.04 (per 3 months) Utility gain for patients on oral chelation: 0.03 (per 3 months)

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Table 4. Continued

Author, year	Population, region	Instrument/method	Treatment	Utility values
McLeod et al[25]	Patients with β-thalassemia major or SCD undergoing frequent blood transfusion, UK	Assumed by the authors	Chronic blood transfusion ICT	Mean utility for deferoxamine/ desferrioxamine administered via a balloon infuser: 0.70 Mean utility for patients receiving deferiprone: 0.76
Spackman et al[22]	Patients with SCD undergoing elective surgery, UK	Derived from their own empirical study Assumed by the authors	Preoperative transfusion	Same values from their own empirical study (see above) Utility decrement for transfusion complication (eg, hepatitis B, HIV, hemolytic transfusion reaction, posttransfusion purpura, variant Creutzfeldt-Jakob disease, hepatitis A, or malaria): 0.05
Blood transfusion: QALY-based comparative effectiveness study				
O'Brien and Hankins[26]	Children with SCD No specific country	Clinician opinion Based on literature	Chronic blood transfusion	Utility for patients on chronic transfusion with severe disease and iron overload: 0.55 (range 0.35-0.75) Utility for patients on chronic transfusion with no severe disease and with iron overload: 0.75 (range 0.55-0.95) Utility for patients on chronic transfusion with severe disease and with no iron overload: 0.60 (range 0.40-0.80) Utility for patients on chronic transfusion with no severe disease and with no iron overload: 0.80 (range 0.60-1.00)
Pharmaceuticals				
O'Brien and Hankins[26]	Children with SCD No specific country	Clinician opinion Based on literature	Hydroxyurea	Utility for patients on hydroxyurea with severe disease: 0.65 (range 0.45-0.85) Utility for patients on hydroxyurea with no severe disease: 0.85 (range 0.65-1.00)

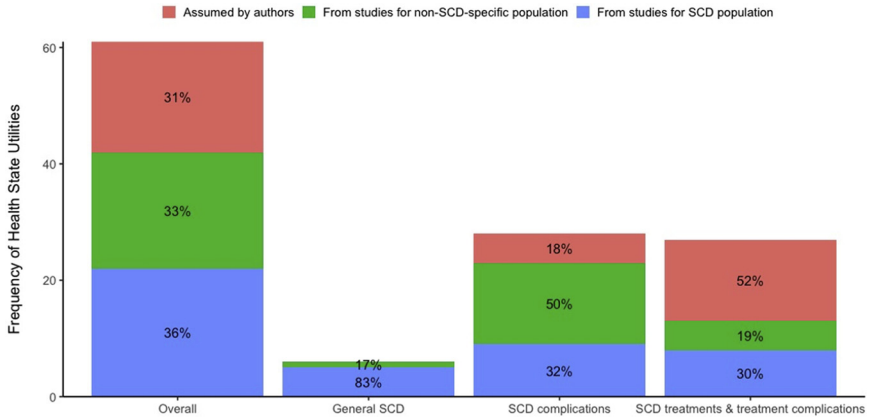
alloHSCT indicates allogeneic hematopoietic cell transplantation; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; HSU, health state utility; ICT, iron chelation therapy; SCD, sickle cell disease; SF-6D, Short Form-6 Dimension; UK, United Kingdom; USA, United States.

Transfusion

Two empirical HSU studies[21,22] and 4 QALY-based outcome research studies[22,24,25] reported HSUs in patients receiving transfusions. The mean HSU value for the empirical studies ranged from 0.55 to 0.854. The 0.55 was reported in the empirical study that measured HSUs for patients who were receiving chronic transfusion and also receiving iron chelation therapy.[21] The 0.854 was reported in an RCT that investigated whether preoperative transfusion decreases the risk of perioperative complications in patients with SCD undergoing low- or medium-risk surgery.[22]

In the QALY-based outcomes research studies, various types of utility decrements were included. Two studies included HSUs for the patients on transfusion without transfusion complications.[24,26] Three studies included HSUs related to iron overload—1 study included HSUs for patients with and without iron overload,[26] and 2 included HSUs associated with treatments for iron overload, such as subcutaneous or oral chelation,[24] deferoxamine or desferrioxamine, and deferasirox.[25] A separate study assumed a utility decrement if patients had any of the following transfusion complications: hepatitis B, HIV, hemolytic transfusion reaction, posttransfusion purpura, variant Creutzfeldt-Jakob disease, hepatitis A, or malaria.[22]

Figure 2. Distribution of sources of the health state utilities used in the outcome research studies. SCD indicates sickle cell disease.



Pharmaceuticals

One QALY-based outcomes research study included HSUs for patients on hydroxyurea with (0.65) and without severe disease (0.85).[26]

Critical Appraisal

The quality assessment for the empirical HSU studies can be found in Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.08.002. Most of the empirical HSU studies reported the variability of their estimates.[18,20-22] Three studies reported the response rate to the instruments used[19,21,22]; one of the studies had a relatively low response rate (approximately 50%).[19] Only 1 RCT study reported loss to follow-up, which was <20%.[22] Finally, 2 studies provided the methods for handling missing data.[20,22]

Figure 2 illustrates the distribution of sources of HSUs used in the QALY-based outcomes research studies. Overall, only 36% of the HSUs were elicited from individuals with SCD. In particular, 83% of the HSUs associated with general SCD were based on studies wherein HSUs were elicited from those with SCD, 50% of HSUs associated with SCD complications relied on studies where in HSUs were elicited from a non-SCD-specific population, and 52% of the HSUs associated with SCD treatments or treatment complications were based on researchers' assumptions (including clinician opinion).

Discussion

To the best of our knowledge, our study is the first to comprehensively summarize and catalog HSUs for SCD and its specific complications and HSUs tied to its treatments. We found a sparsity of literature that empirically estimated HSUs in individuals with SCD. In the QALY-based outcomes research studies, only 36% of the HSUs were obtained from the empirical studies conducted in the SCD population.

The limited number of studies we found did not fully address the complexity of the disease—HSUs for many complications were not measured at all, and complications that were represented as HSUs were not assessed in a time-varying fashion. In particular, we found no United States-based empirical HSU study for general SCD or for SCD complications. Most of the empirical studies did not assess HSUs by age. This is a gap, because it will be important to have age-specific estimates because the rate and spectrum of complications can vary throughout a patient with SCD's lifecourse.[28] Furthermore, compared with the comprehensive list of complications we established in our PICOTS criteria (Table 1), our analysis suggests that utilities of many SCD complications have not yet been studied empirically (eg, stroke, infections, priapism, hepatobiliary complications, and splenic disease).

Possibly owing to the scarcity of empirical HSU data for SCD complications, QALY-based outcomes research studies often relied on assumptions or HSU estimates from non-SCD-specific populations, even for some typical complications. For example, stroke is a common acute complication in the SCD population—historically 10% of children with SCD experience a symptomatic stroke.[29] Nevertheless, the HSUs associated with stroke were either assumed or obtained from studies that elicited HSUs from individuals with stroke or type 2 diabetes mellitus in those without SCD.[23,24] Similar to the research gap identified in the empirical studies, the utility loss owing to many other SCD complications was not considered in published QALY-based outcomes research studies.

Similarly, the empirical studies related to SCD treatments did not explicitly assess the utility decrements attributable to the treatment complications, such as GVHD, iron overload, and alloimmunization (although 1 study estimated mean HSU among patients receiving iron chelation therapy for treating iron overload[21]). No empirical studies were found for patients receiving a specific drug therapy. Moreover, the empirical studies did not report HSUs at various time points after treatments. Some complications may occur long after the treatments are administered. In most of the QALY-based outcomes research studies, the utility decrements attributable to the treatment complications were not modeled. Only 1 CEA and 1 comparative effectiveness study considered the treatment complications, yet their estimates were based on assumption or clinician opinion.[22,26]

Our review and findings of HSUs used in CEA models echo the concerns raised by the Good Practices for Outcomes Research Task Force of the International Society of Pharmacoeconomics and Outcomes Research.[17] This report states that when HSUs are obtained from the literature for use in CEAs, caution should be exercised to address issues such as relevance of the patient population, sources of the HSUs used, and their method of elicitation.[17] The Task Force also suggests that good practice requires a systematic review of existing literature to identify these HSU values.[17] Our catalog identifies the gaps in the existing HSU literature in the context of SCD. As such, it provides a path forward to future empirical work.

Furthermore, the Second Panel on Cost-Effectiveness in Health and Medicine recommends that the spillover effects of disease on family members should be incorporated into CEAs.[30] Studies have

shown that SCD has a notable impact on the HRQoL of caregivers of patients with SCD.[31,32] Treatments that help ease the symptoms of patients with SCD can also relieve caregiver burden. Neglecting this effect in CEAs may underestimate the value of SCD interventions. Quantifying HSUs among caregivers of patients with SCD could be another focus of future empirical HSU studies.

Our study has several key strengths. First, it is comprehensive. By using rigorous methods, we identified not only the HSUs elicited in the empirical studies but also the HSUs used in outcome research studies, which were either from published literature or based on authors' assumptions. We made a concerted attempt to track HSUs back to their source and to validate these by replicating the calculations. Second, we categorized the HSUs as general SCD without specifying complications, SCD complications, and SCD treatments, which are the key clinical inputs necessary for developing a SCD CEA model. This will facilitate the inclusion of HSUs in future QALY-based modeling studies.

Our study also has several limitations. First, our systematic review was limited to articles published in English, and abstracts and conference presentations were not included. Second, we did not include studies published before 2008. Nevertheless, we found 1 cost-effectiveness study published in 2009 that relied on HSUs for the thalassemia population[25] and 1 comparative effectiveness study published in 2009 that assumed HSUs based on clinician's opinion.[26] These data suggest that the availability of empirical HSUs studies before 2008 might be sparse. Finally, we did not systematically search the HSU studies for thalassemia, although some of the HSUs were found from the included CEAs. HSUs associated with thalassemia treatments, such as therapy for transfusion-related iron or gene therapy could be a surrogate, if the data for SCD are not available.

In summary, our findings highlight the dearth of empirical studies that elicited HSUs for SCD. Empirical studies should be conducted to elicit HSUs from individuals with SCD using direct or indirect methods. These studies should capture HSUs that reflect one or more specific complications or receipt of a specific treatment. Estimations of these by age groups and time frames after treatments would be of value. Moreover, to provide a complete picture of the burden of SCD, HSUs should be elicited from patients' caregivers. These HSU data can be collected both alongside clinical trials and in cohort studies.[33-36] CEA models informed by these newly elicited utilities will more accurately reflect lifetime experiences of patients with SCD and the value of emerging curative therapies.

Conclusions

We developed a comprehensive catalog of HSUs associated with SCD from the published literature. Our catalog will benefit future modelers of CEAs of disease-modifying and curative therapies for SCD.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2021.08.002.

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