CureSCi CDE Project
Outcomes Working Group

The goals of the Cure Sickle Cell Initiative (CureSCi) CDE project is to support the NIH roadmap and address challenges of varied data collection standards and difficulties in comparing between studies and poor definitions around the specific data elements collected. CDEs are recommended by the NIH Strategic Plan for Data Science improving data quality, facilitating collection of data, data-sharing and comparison and reducing study start-up time and overall study cost.

The Outcomes Working Group (WG) has drafted the set of recommended instruments through the following approach:

- A comprehensive list of measures believed to be relevant to SCD was developed, partly drawing on the prior work of the ASH/FDA End Points for SCD Clinical Trials workgroups[1].
- The list of measures was divided into coherent domains – Pain, Affective, Fatigue and Sleep, Functional, Cognitive, and General Health/Quality of Life.
    - In several domains, relevant sub-domains were identified; such as pain intensity and pain impact.
    - For each domain/subdomain, often several reasonable candidate instruments were available.
- Subgroups of the panel reviewed measures for each domain, presenting the results to the entire panel at meetings or through shared digital workspaces.
    - Some instruments were deprecated due to relevance – for example, measures judged to be primarily used to screen for/quantify severity of major depressive disorder were not included in favor of instruments developed to measure the emotional impact of SCD.
- The panel examined measures for reliability and validity; particularly whether validated in SCD and for whether they were likely to be sensitive to clinically significant changes.
- The consensus of the panel was that -- all else being equal -- instruments developed and validated in SCD were to be preferred over those that had not been validated in SCD, or those with some validation work in SCD but not specifically developed to measure SCD-relevant outcomes. However, in several cases, other factors suggested that non-SCD specific instruments might be useful; and there may certainly be studies in which such instruments could be preferred.
- The panel reached consensus on categorization of instruments as core, highly recommended, supplemental, or exploratory by discussion, research by individuals and subgroups, and repeated rounds of voting.

The WG was also asked to consider and address the differences between target population (e.g., adult and pediatric) and the specificity to SCD patients. For Patient-Reported Outcomes (PROs), several batteries with measures at least partially validated in SCD were available. These included PROMIS, ASCQ-Me, and PedsQL SCD Modules. In general, PROMIS measures were more general, applicable across multiple age groups, and could facilitate comparisons in outcomes with non-SCD conditions. ASCQ-Me[2,3] and PedsQL's SCD module[4,5] were developed and validated specifically for SCD, and there is some evidence that ASCQ-Me at least may capture more disease-relevant information than similar

measures included in PROMIS[6]. However, ASCQ-Me and PedsQL SCD Module measures differ, and are validated in different age groups (adult and pediatric, respectively).

Patients, caregivers, and advocates on the panel were strongly of the opinion that a measure of overall health and/or quality of life should be included as a core measure. Measures in this domain all included items redundant with other measures, including some that are core and highly recommended; such as mood, pain, and function. Recommendations on this domain were a matter of long discussion; and a number of very good candidate instruments were considered. Factors weighed included accessibility, participant burden, suitability to extract preference-based utilities for cost-utility estimations, and applicability to SCD. At the end of this process PROMIS Global Health measures were selected as core measures of global health. Strengths of the PROMIS system included accessibility, ability to be administered by multiple methods, modest participant burden, availability of child and parent-proxy measures, and item-level validation. Regarding the last point, the global health and quality of life items from these PROMIS measures may be useful as simple and validated measures of clinically significant global improvement.

In considering issues unique to SCD, the WG considered that the most robust evidence for treatment effects in SCD is in stroke prevention and reduction in acute care visits for painful crises[7–10]. The natural history of many other important SCD symptoms and impairments is not well understood. Chronic/non-crisis pain and cognitive dysfunction have complex causes and their overall course and response to treatment are poorly defined[11–14]. While each can occur without other detectable complications of SCD, each may also be a consequence of such complications – as in the cases of cognitive dysfunction due to stroke[15] or chronic pain due to avascular necrosis of bone. **Whether the expected outcomes for these problems should be non-progression, improvement, or remission is not established**; and it is likely that degrees of improvement may differ for relevant subpopulations – such as patients with AVN or more severe anemia. Therefore defining “degrees of cure” on these measures for the moment is highly speculative.

As SCD is a condition that involves both acute and chronic pain, the construction of pain intensity outcome measures may differ depending on the outcome of interest, partly depending on considerations of its expected time course. While the VAS and NRS scales are cross-sectional measures of pain intensity, clinical trial outcome measures likely will involve change in pain intensity. In other conditions, clinically important changes have been defined as differences between initial and final pain during the study, or percentage change in pain intensity from baseline, and this is an important means for clinicians to evaluate clinical relevance of study outcomes. With placebo/sham control studies, comparisons between groups at individual time points or time-by-treatment interaction terms may also be useful to report.

In addition to defining natural history of symptoms and impairments as beforementioned, other areas of unmet needs in SCD were discussed. Many validation studies for SCD-related measures were shown to differentiate disease exacerbations (periods of hospitalization or crisis) from baseline and/or patients with more severe disease from those with less severe disease[16,17]. Their sensitivity to more moderate or slow changes in illness, such as partial improvement from treatment and long-term changes in chronic symptoms, is largely unproven.

While the panel reached consensus on important symptoms and impacts of SCD, their relative priority to patients needs further study. This made decisions about defining core measures difficult. For example, while fatigue is frequently cited by patients with SCD as a major problem, the amount of evidence available on its prevalence, severity, impact, and effect on quality of life is severely lacking relative to acute care utilization, painful crises, and pain in general. The inclusion of measures of fatigue as core outcomes was based heavily on the recommendation of patient/caregiver/advocate panel members and the clinical experience of the clinicians of the panel.

There are some domains of symptoms and impairments that are common and clinically significant, but for which agreement on optimal measures are lacking. For example, cognitive function and more specifically processing speed and executive function were cited as important domains. However, studies have used different measures[12,18]; and how these compare to each other, the natural history of cognitive dysfunction, and how they predict patient-relevant life problems are still unsettled. Therefore, recommendations in this area were driven largely by pragmatic considerations, such as cost of measures and necessity for highly specialized staff for their administration.

Patient/Advocates

Those living with SCD, caregivers, and those who have received curative therapies were involved in initial phases of evaluating prospective instruments/elements to include in the outcome findings and participated in discussions that lead to the narrowing and finalization of the list of instruments. Persons directly impacted by SCD provided feedback on the instruments/elements to be utilized and offered their lived experiences as well as the experiences of others within the SCD community. SCD community members of the WG also selected elements to be included in the final recommendations.

In careful review of the instruments, SCD community members also provided feedback regarding burden/acceptability when making final recommendations. The WG was able to make recommendations that captured diversity and complexity. However, because many of the instruments utilized were generated with data from disease states presenting similar symptoms experienced by those living with SCD, there were some limitations capturing the complexity of clinical presentations that are specific to SCD. There was also a degree of difficulty assessing certain elements as core/supplemental/highly recommended (e.g., elements addressing pain and fatigue). Although certain measures may not have been categorized as core, the SCD community WG participants would like to emphasize that the measures graded supplemental - highly recommended are also important to the final recommendations.

In regard to other unmet needs, there is a need for a specific instrument that will assist with categorizing pain to determine a “degree for a cure.” (chronic or acute? Does pain stem from SCD-related complications or other factors?). There was difficulty finding many instruments/elements that addressed SCD specifically. This presented some challenges and opportunities. The completion of these recommendations will address many of them by creating a source of outcome measures that are SCD-focused. In addition, measures assessing pain/fatigue/QoL during the transition period from pediatric to adult care are needed for children, due to the lengthy follow-up period after the completion of a curative therapy. This will greatly assist in assessing the progression of future adult curative therapy cohorts.

Summary recommendations

Subdomain	Population	Instrument Name	Classification	Notes
Pain Intensity	Adults, children 8 years old and above	Numeric Rating Scale (NRS)	Core	With appropriate time anchors and serial measures for chronic and acute pain.
Pain Intensity	Adults, 8 years old and above	Visual Analog Scale (VAS)	Supplemental	The panel considered the Numeric Rating Scale to be more easily administered by a broader range of means, to require less equipment, and to be more generalizable to clinical practice. However, the VAS has certain favorable measurement properties and arguments could be marshalled for its use in some studies.
Pain Impact/ Interference	Adults	ASCQ-Me Pain Impact	Core	Preferred if the study population are adults.
Painful Crises	Adults, specific to SCD	ASCQ-Me Pain Episodes	Core	Preferred if the study population are adults
Pain Impact/ Interference	Children ages 5–18 years, specific to SCD.	PedsQL Pain Impact SCD module (children)	Core	Preferred if the study population are children. Parent proxy measures are available for ages 2–18 years.
Pain: Mixed	Children ages 5–18 years, specific to SCD	PedsQL Pain and Hurt, SCD modules	Core	Preferred if the study population are children. Parent proxy measures are available for ages 2–18 years.
Pain Impact/ Interference	Children and Adults, not SCD specific	PROMIS Pain Interference; Adult and Pediatric modules	Core	An appropriate alternative measure to ASCQ-Me and PedsQL, should comparison across conditions be highly desirable, or if the study population will involve a mix of adult and pediatric

Subdomain	Population	Instrument Name	Classification	Notes
				participants. If the study population is limited to either adults or children; ASCQ-Me or PEDS-QL measures (respectively) are preferred.
Emotional Impact of SCD	Adults, specific to SCD	ASCQ-Me Emotional Impact	Supplemental, Highly Recommended	
Emotional Impact of SCD	Children, specific to SCD	PedsQL, SCD Module Emotions	Supplemental, Highly Recommended	
Emotional Impact of SCD	Children, specific to SCD	PedsQL, SCD Module Worrying	Supplemental	
Negative Affect: Mixed	Children	PROMIS Pediatric Physical Stress Experience	Supplemental, Highly Recommended	
Low Mood	Children and Adults, not SCD specific	PROMIS Emotional Distress: Depression (Pediatric and Adult)	Supplemental, Highly Recommended	While these measures are not designed to measure the emotional effects of SCD, they are available for broad age ranges and can be used to compare across conditions which might make them appropriate for some study designs.
Anxiety	Children and Adults, not SCD specific	PROMIS Emotional Distress: Anxiety (Pediatric and Adult)	Supplemental, Highly Recommended	While these measures are not designed to measure the emotional effects of SCD, they are available for broad age ranges and can be used to compare across conditions which might make them appropriate for some study designs.
Fatigue	Children and Adults, not SCD specific	PROMIS Fatigue/Pediatric Fatigue	Core	
Fatigue	Children with SCD	PedsQL Multidimensional Fatigue Scale	Core	

Subdomain	Population	Instrument Name	Classification	Notes
Sleep Disturbance	Children and adults, not SCD specific	PROMIS Sleep Disturbance	Supplemental, Highly Recommended	Recommended for children with SCD; and in studies of mixed age
Sleep Disturbance	Adults	Pittsburgh Sleep Quality Index (PSQI)	Supplemental	
Sleep Disturbance	Adults with SCD	ASCQ-Me Sleep Impact	Supplemental, Highly Recommended	Recommended for studies exclusively of adults with SCD
Daytime Sleepiness	Adults, newer scale for children	Epworth Sleepiness Scale (and Epworth CHAD)	Supplemental	Child: http://pulmonary.pediatrics.med.ufl.edu/files/2012/09/epworth-sleepiness-scale-children.pdf
General Function	Adults	Canadian Occupational Performance Measure (COPM)	Supplemental	
Social Function	Adults with SCD	ASCQ-Me Social Functioning Impact	Supplemental	
Physical Function	Adults with SCD	ASCQ-Me Stiffness Impact	Supplemental, Highly Recommended	
Physical Function	Adults	PROMIS - Physical Function - 12a	Supplemental	
Physical Function	Children with SCD	Other PROMIS Physical Function measures, such as PROMIS Upper Extremity and Mobility, available for Pediatrics but not validated for Adults	Supplemental	
Global Health/ Quality of Life	Adults	PROMIS 10 Global Health	Core	
Global Health/ Quality of Life	Children	PROMIS 7+2 Global Health	Core	Parent/Caregiver Proxy measures are also available

Subdomain	Population	Instrument Name	Classification	Notes
Global Cognition	0-3.5 years	Bayley-III	Supplemental	Should global cognition and development be a focus of the study for infants, this would be preferred.
Global Cognition	2.5-7 & 7/12	Wechsler Preschool and Primary Scale of Intelligence WPPSI-IV (+consider WPPSI Cancellation)	Supplemental	Should global cognition and development be a primary focus this will be a reasonable outcome measure; participant burden and resource need should be weighed against more specific measures
Global Cognition	6-16 & 11/12	Wechsler Intelligence Scale for Children (5th Ed) WISC-V	Supplemental	Should global cognition and development be a primary focus this will be a reasonable outcome measure; participant burden and resource need should be weighed against more specific measures
Global Cognition	Adults	Wechsler Adult Intelligence Scale WAIS-III	Supplemental	Should global cognition and development be a primary focus this will be a reasonable outcome measure; participant burden and resource need should be weighed against more specific measures
Global Cognition	3-6, 1-17, and 18+ Depending on Battery	NIH Toolbox	Supplemental, Highly Recommended	Generally preferred over other cognitive measures due to minimal resource requirements, rapid administration requiring modest training, and inclusion of relevant subscales (such as processing speed).
Executive Functioning (and Attention)	Versions for 3-7, 8-11, and 12+	NIH Toolbox: Flanker Inhibitory Control and Attention Test	Supplemental, Highly Recommended	NIH Toolbox measures generally preferred over other similar measures due to low participant burden and minimal resource requirements, as well as broad age ranges.

Subdomain	Population	Instrument Name	Classification	Notes
Executive Function	Versions for 3-7, 8-11, and 12+	NIH Toolbox: Dimensional Change Card Sort Test	Supplemental, Highly Recommended	NIH Toolbox measures generally preferred over other similar measures due to low participant burden and minimal resource requirements, as well as broad age ranges.
Executive Function	9 and up	Trail Making Test, parts A and B	Supplemental	
Executive Function	8-89 years	Delis-Kaplan Executive Function System D-KEFS	Supplemental	
Executive Function	6 years, 5 months to 89	Wisconsin Card Sort Test	Supplemental	
Processing Speed	Age 7+	NIH Toolbox: Pattern Comparison Processing Speed Test	Supplemental, Highly Recommended	NIH Toolbox measures generally preferred over other similar measures due to low participant burden and minimal resource requirements, as well as broad age ranges.
Processing Speed	Adults	Processing Speed Index (of WAIS-III)	Supplemental	
Working Memory	7+	NIH Toolbox: List Sorting Working Memory Test	Supplemental, Highly Recommended	NIH Toolbox measures generally preferred over other similar measures due to low participant burden and minimal resource requirements, as well as broad age ranges.

Exploratory Measures

Domain	Measure	Comments
Pain Mechanism	Quantitative Sensory Testing	If a study involves a hypothesis as to neural (and other) mechanisms of changes in pain, quantitative sensory testing may provide additional supporting evidence.
Sleep Impact/Sleep Disturbance	Polysomnography	If a study involves hypotheses as to mechanisms or physiologic correlates of sleep disturbance or sleep interference, polysomnography may provide additional evidence.
Life Satisfaction	PROMIS Pediatric Item Bank Life Satisfaction (Short Form 4a)	Life Satisfaction might be of interest beyond general health and quality of life in some studies.
Stigma	Measure of Sickle Cell Stigma	Stigma is often reported as a distressing psychological and social aspect of SCD, and the effect of curative therapy on this may be of interest in some studies.
Coping Skills / Pain Coping	Coping Strategies Questionnaire – Revised for SCD	Assessing changes in coping, as well interactions between coping styles and treatments or treatment selection, may be of interest in some studies.
Caregiver Burden	Caregiver Burden Scale	While the primary outcomes of curative therapies should center on the person with SCD; the effects on families and caregivers can be serious and improvements in this domain may be important to document.

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