CURE SICKLE CELL.

CureSCi CDE Project
Physical Examination/Medical History Working Group

The goals of the CureSCi CDE project are 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 group reviewed existing forms and develop needed modules, assign classifications to their use:

- Core data elements are essential to all studies for the domain
- Supplemental-Highly Recommended
- Supplemental are data elements that depend on study design and protocol
- Exploratory data elements may fill current gaps but have limited validation

Note: The group did not develop definitions of conditions (e.g., ACS).

After some deliberations, the Physical Examination/Medical History Working Group (WG) defined the following modules to be within their scope:

1. Sickle Cell Disease Related Pain Episodes – VOCs (acute care utilization)
2. Laboratory Tests
3. Medical History Form
4. Reproductive History Form (Endocrine, Fertility and Bone CRF)
5. Acute (Note: Areas below may be captured in Monitoring Side Effects Working Group modules)
    a) Infection (non-specific)
    b) Priapism
    c) Acute anemia
    d) Hepatobiliary Complications
    e) Splenic sequestration
6. Chronic conditions:
    a) Severe/chronic anemia
    b) Chronic pain (opioid use and analgesic use related on #9 while PROs will be in Outcomes WG)
    c) Liver disease
    d) Spleen disease
    e) Avascular necrosis and bone damage
    f) Leg ulcers
    g) Proliferative retinitis/retinopathy
    h) Malnutrition, delayed puberty and reduced growth
7. Behavioral History or Alcohol and Tobacco Use, Substance Abuse
8. Hospitalization History
9. Prior and Concomitant Medications
10. General Physical Examination Form

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Patient Advocates Input

The SCD patients/caregivers/advocates in the working group were given opportunities to attend zoom meetings to discuss the outline with other team members. They were asked for their input and given opportunities to share their thoughts.

In order to consider and factor in the experiences of people with SCD in making recommendations, the working group tried to use their own experiences with patients and knowledge of research in making recommendations that would provide best outcomes for individuals and families impacted with SCD. The medical experts on the working group expressed concern and interest in the sickle cell community throughout their deliberation.

There was consideration on making sure the case report forms or instruments were patient-friendly if they were patient reported and try to be acceptable for people with SCD and the SCD community. The group also tried to capture the diversity and complexity of the clinical presentation of SCD.

There are still specific needs and gaps that should be considered. It is hard to do but consideration must be given to the variance of how people experience pain. From experience of caregivers, there are times that SCD patients can tolerate amazing levels of pain. As a result, the degree of urgency of SCD patient needs may be underestimated based on rating of their pain based on the scales often used particularly with children. One suggestion would be to have a scale for parents to assess their observations of pain in their children. Something such as "when considering how your child typically manages pain, how would you rate what she/he is feeling right now?" This could helpful and could be used in general assessments as well. As a reminder, the medical professionals need to see the data and lab results and not how the child may present themselves since that is often deceiving in SCD patients.

In addition, there should be more efforts to address mental health needs of patients AND family members. Having a chronic illness is stressful and can be depressing for many. The sickle cell community is encouraged by the proclamation that we are warriors, but this can lead to people feeling pressured to portray emotional/mental strength even when they really need support.

There should be assessments for medical trauma as well. It is not apparent if there is data that address the medical trauma of sickle cell disease and how it intersects with the decision of care and treatment. There does not appear to be any tools for this or language that identifies medical trauma which could be significant within the sickle cell community. Medical trauma is very real and the lived experiences of how decisions are or are not made, weigh heavily on families as they make choices. They may consider if that decision will produce negative or positive outcomes and if the choice produces something that maybe perceived as aspects of trauma and how that perception will impact treatment, education, social interaction, behavior, cognition development, and other elements of quality of life.

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Table Summary:

Domain/Subdomain	CRF	Classification	Notes
Assessments and Examinations / Acute Conditions	Acute Pain Episode	Core and Supplemental	Core elements: Last 12 months, care due to vaso-occlusive crisis, number of inpatient admissions, number of treat and release, ED visits and days hospitalized.
Assessments and Examinations / Acute Conditions	Acute Anemia	Core and Supplemental	Lab Values, cause, transfusion and associated conditions data elements for each episode and changes since baseline on this module
Assessments and Examinations / Chronic Conditions	Chronic Anemia	Core and Supplemental	Core Baseline Values. EPO level is Supplemental
Assessments and Examinations / Chronic Conditions	Chronic Pain	Core and Supplemental	Core: Has the patient had at least 15 days/month with pain for at least 6 months? Does the patient display at least 1 on the following signs (type "x" in box next to item if applicable to patient): a. Palpation of the region of reported pain elicits focal pain or tenderness b. Movement of the region of reported pain elicits focal pain c. Decreased range of motion or weakness in the region of reported pain d. Evidence of skin ulcer in the region of reported pain e. Evidence of hepatobiliary or splenic imaging abnormalities (e.g., splenic infarct, chronic pancreatitis) consistent with the region of reported pain f. Evidence of imaging abnormalities consistent with bone infarction or avascular necrosis in the region of reported pain *If either question above is Yes, then patient has "chronic pain".*

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Domain/Subdomain	CRF	Classification	Notes
Assessments and Examinations / Acute and Chronic Conditions	Hepatobiliary Complications	Supplemental	
Assessments and Examinations / Acute and Chronic Conditions	Leg Ulcer, Retinopathy and Avascular Necrosis	Supplemental	Assessments of chronic leg ulcer, retinopathy or avascular necrosis since last reported.
Assessments and Examinations / Acute Conditions	Acute Spleen	Core and Supplemental	Acute splenomegaly (as defined by Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG) Follow-up Observational Study II Protocol)
Assessments and Examinations / Chronic Conditions	Chronic Spleen	Core and Supplemental	Definitions from (BABY HUG): Splenomegaly definition >= 2 cm increase in spleen size since last visit. The details on spleen size and function are Supplemental
Assessments and Examinations / Chronic Conditions	Chronic Malnutrition	Core and Supplemental	Core: Height/Weight/BSA/BMI Percentile of BMI for age/adult
Assessments and Examinations / Chronic Conditions	Malnutrition Identification Guide	Guideline	Definitions for the Malnutrition CRF and other guidelines.
Assessments and Examinations / Chronic Conditions	Endocrine, Fertility and Bone	Core and Supplemental	Core elements on Avascular necrosis and fertility preservation questions.
Assessments and Examinations / Acute Condition	Priapism	Core and Supplemental	Core CRF and other patient reported outcomes which are Supplemental including: Priapism Impact Profile PRO adult and modified version for minors.
Participant History and Family History	Medical History Core	Core	Derived electronic medical history along with questionnaires at baseline include disease/disorders and ailments Muscle, Bone, Joint, Heart, Kidney/Urinary/Genital, Liver, Spleen, Lung, Neurological Problems, Blood Problems Other Than Sickle Cell, Infection, Thrombosis, Other Disease/Ailments, Psychological/Mental Health
Participant History and Family History	Medical History Supplemental	Supplemental	Include Skin Ulcer, Endocrine and Immunological conditions.

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Domain/Subdomain	CRF	Classification	Notes
Participant History and Family History	Transfusion History	Core and Supplemental	Core: Transfusion in lifetime indicator; RBC alloantibodies; Number of transfusions in lifetime.
Participant History and Family History	Behavioral History Core	Core	General Smoking, Alcohol and Drug Use History questions
Participant History and Family History	Behavioral History	Supplemental	More details questions and includes questions on vaping from National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General [Internet]. Atlanta (GA): Centers for Disease Control and Prevention (US); 2016. Chapter 2, Patterns of E-Cigarette Use Among U.S. Youth and Young Adults. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538687/
Participant History and Family History	Surgical History	Core	General history of surgical procedures
Participant History and Family History	Hospitalization Form	Core	Form from the Silent Cerebral Infarct Multicenter Transfusion (SIT) Trial
Treatment and Intervention Data / Prior and Concomitant Medications	Prior and Concomitant Medications	Core and Supplemental	Core CDEs related to hydroxyurea and pain medications.
Treatment and Intervention Data / Prior and Concomitant Medications	PROMIS Scale – Medical Adherence	Exploratory	Peipert, J. D., Badawy, S. M., Baik, S. H., Oswald, L. B., Efficace, F., Garcia, S. F., Mroczek, D. K., Wolf, M., Kaiser, K., Yanez, B., & Cella, D. (2020). Development of the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) Medication Adherence Scale (PMAS). Patient preference and adherence, 14, 971–983. https://doi.org/10.2147/PPA.S249079
Participant Characteristics	Education – School Questionnaire	Core for Pediatrics	Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG) https://www.phenxtoolkit.org/protocols/view/840201

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Participant Characteristics	Demographics	Core and Supplemental	Core: Sex, Gender, Date of birth, Ethnicity and Race
Participant Characteristics	Social Status	Core and Supplemental	Core: Years of education
Participant Characteristics	Social Determinants	Supplemental	Montefiore-Einstein Social Determinants of Health Screen
Participant Characteristics	Adverse Childhood Experiences	Exploratory	Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998 May;14(4):245-58. doi: 10.1016/s0749-3797(98)00017-8. PMID: 9635069.
Assessments and Examinations / Laboratory Tests	Laboratory Tests	Core and Supplemental	Many elements are Core and standard of care.
Assessments and Examinations / Physical Examination	Physical Examination	Core and Supplemental	Core: Date of Exam, Body System, Result (each body area examined for abnormal findings)
Assessments and Examinations / Physical Examination	Vital Signs and Blood Gases	Core and Supplemental	Core: Heart Rate, Blood Pressure, Oxygen saturation, Respiratory rate in breaths per min (see PhenX protocols to be referenced)
Participant Characteristics	Psychosocial Assessment Tool for Medical Trauma	Supplemental	Reader SK, et al. Psychosocial Screening in Sickle Cell Disease: Validation of the Psychosocial Assessment Tool, Journal of Pediatric Psychology, Volume 45, Issue 4, May 2020, Pages 423–433, https://doi.org/10.1093/jpepsy/jsaa002 Reader SK, et al. (2017). Caregiver perspectives on family psychosocial risks and resiliencies in pediatric sickle cell disease: Informing the adaptation of the Psychosocial Assessment Tool. Clinical Practice in Pediatric Psychology, 5(4), 330–341. https://doi.org/10.1037/cpp0000208

Classification Definitions:

Core: Data element that collects essential information in domain based on the current clinical research best practices. These have been used and validated in SCD and are required for the specified study design, protocol or type of research involved.

Supplemental-Highly Recommended: Data element that is important for study design or protocol but not required for collection.

Supplemental: Data element which is commonly collected in clinical research studies. Use depends upon the study design, protocol or type of research involved.

Exploratory: Data element that requires further validation but may fill current gaps and/or substitute for an existing element once validation is complete. Such data elements show great promise but require further validation before they are ready for prime-time use in clinical research studies.

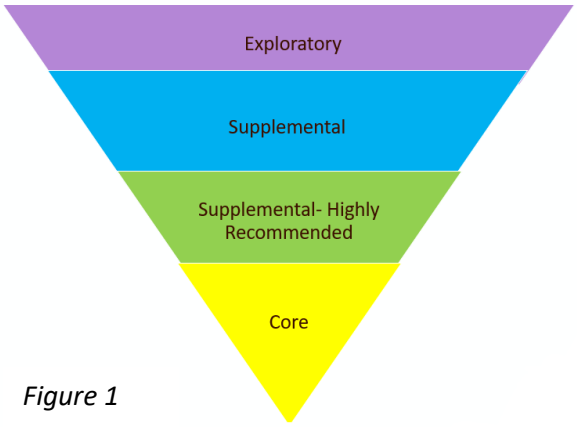

Figure 1