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CureSCi CDE Project
Cardiopulmonary, Renal and Cerebrovascular 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. Common data elements (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:
Disease Core: Data element that should be collected in all clinical research genetic studies in SCD. It is anticipated that investigators will need to collect the disease Core CDEs.
Core: Data element that collects essential information in domain based on the current clinical research best practices. These have been used and validated and are required should the study design involve this domain as an important study area or target outcome.
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.

The group did not develop definitions of conditions if there is not one already existing.

The following forms were reviewed among others:

1. Treatment of Pulmonary Hypertension and Sickle Cell Disease With Sildenafil Therapy walk-PHaSST (https://clinicaltrials.gov/ct2/show/NCT00492531, https://curesicklecell.rti.org/Study/Details/67 (forms on site))
2. Sleep and Asthma Cohort (SAC) Study (https://curesicklecell.rti.org/Study/Details/68)
3. CRFs from Dr. Jeffrey Lebensburger: 24 HR BPM, Urine Biomarker and Annual Cohort Visit Lab Tests
4. Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG) Follow-up Observational Study II Protocol (BABY HUG) - https://clinicaltrials.gov/ct2/show/NCT01783990

The group split out their task into the following areas:

1. Acute Chest Syndrome
2. Echocardiogram
3. Functional Cardiac Outcomes
4. Cardiac MRI
5. Glomerular Filtration Rate
6. Albuminuria or Proteinuria
7. Renal Ultrasound
8. Urine concentrating Ability

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9. Asthma Outcomes and Medication
10. Pulmonary Function Test
11. Lung Disease
12. Sleep (See separate summary)
13. Cerebrovascular (See separate summary)

The groups utilized the ASH-FDA recommendations along with previous study forms to gather the appropriate CDEs for these recommendations. Under consideration were the tables below from *Blood Adv* 2019; 3 (23): 4002–4020

Table 1. End points for renal complications associated with SCD

Condition	End point	Test	Outcome/outcome measure	Type of end point	Ages
CKD, albuminuria	Albuminuria or proteinuria	First morning void or 2 consecutive untimed albumin/creatinine ratio or protein/creatine ratio	Percent decline in albuminuria	Direct: severe albuminuria; surrogate: moderate albuminuria	All age groups
CKD, GFR	Renal replacement therapy	Initiation of renal replacement therapy (may differ based on clinical practice)	Percentage of patients who require initiation of renal replacement therapy	Direct	All age groups
CKD, GFR	GFR	Measured GFR and estimated GFR	Percentage of patients who progress in stage of CKD or percentage of decline in GFR	Surrogate	Adults
Hypertension	Cardiovascular end point	Clinically defined	Number of patients who develop stroke, myocardial infarction, death	Direct	All age groups
Hypertension	Systolic or diastolic blood pressure; pediatric studies should consider use of ambulatory blood pressure monitoring	Blood pressure measurement	Change in systolic or diastolic blood pressure (5 mm Hg)	Future	All age groups
Hyposthenuria	Urine concentration availability	Water deprivation test; not >10 h in children; meaningful tests are those concentrating urine >500 mOsm/kg H_2O	Percentage of patients with preservation of urine concentration ability	Surrogate	Infants or toddlers
Kidney injury	Acute kidney injury defined by serum creatinine or urine output; biomarker of kidney injury	Serum creatinine or urine output; novel biomarkers of kidney injury (eg, NGAL, KIM-1)	Percentage of patients who develop acute kidney injury; reduction in urine biomarkers (25% change)	Future	All age groups

KIM-1, kidney injury molecule 1; NGAL, neutrophil gelatinase-associated lipoprotein.

Table 2. End points for cardiovascular complications associated with SCD

Condition	End point	Test	Outcome/outcome measure	Type of end point	Ages
PH and risk of death	Right heart catheter defined PH	RAP, CI, mPAP, and PVR	Percent change in RAP, CI, mPAP, TPG, or PVR	Direct: RAP, mPAP, CI; surrogate: PVR	Adults
PH and risk of death	TRV	Doppler echocardiography	TRV ≥3.0 m/s or TRV ≥2.5 m/s and NT-pro-BNP level >160 pg/mL	Surrogate	Adults
PH and risk of death	Composite model	Doppler echocardiography, NT-pro-BNP, and 6-min walk test	TRV >2.5 m/s, NT-pro-BNP level ≥160 pg/mL, and 6-min walk test <330 m	Surrogate	Adults
Diastolic dysfunction	E/e' and E/A; myocardial fibrosis	Echocardiogram; cardiac MRI	Percent improvement toward normal	Future	All age groups
Functional exercise capacity	Walk distance	6-min walk test	Change in distance walked (30-40 m)	Direct	Adults
ACS	Incidence using an accepted definition; progression using an accepted definition	Clinically defined	Percentage of patients who develop ACS; percent of patients that clinically worsen; respiratory support, O_2 requirement, transfusion therapy	Direct	All age groups
Asthma	Development of ACS, pain event, or asthma exacerbation	Clinically defined	Time to event in incidence of ACS, pain crisis, or use of rescue inhaler (number of events/days using rescue inhaler) low FEV_1 at baseline	Direct Indirect	All age groups
Thromboembolism	Pulmonary embolism, VTE	Clinically defined thrombus	Percentage of patients with either pulmonary or VTE	Direct	All age groups

FEV_1, forced expiratory volume in 1 second; MRI, magnetic resonance imaging.

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****Patient Advocates Only****

Caregivers, advocates, and family members of patients with sickle cell disease were involved in drafting recommendation from the beginning of this project. Many of the advocates also were medical professionals and/or had research experience. These members were able to provide rich input on how these recommendation impact both the patient and medical providers. Advocates played an integral role in selection of measures and provided input on how inclusion of certain measures may benefit patients and how measures were classified.

The subgroup considered the experiences of people with SCD by considering the physical burden, anxiety, time, and financial burden of obtaining certain measures. When making recommendation the subgroup considered the evidence, risks, and benefits associated with each test. The subgroup considered potential complications people with SCD may experience while receiving curative therapies and included recommendations on the best ways to evaluate patients to detect complications early.

The subgroup considered the burden associated with the length and number of questionnaires, effort required to complete patient-reported outcomes, potential anxiety associated with imaging and procedures. The time burden of completing these measures was also considered and along with the potential benefits. A structured classification system was used to prioritize measures.

The subgroup was made up of a diverse population of patient advocates and physician-scientists from various medical subspecialties, regions, and institutions. This provided for diverse perspectives on the various organ-specific complications, clinical presentations, and evaluations of SCD complications.

There is a great need for more validated instruments to objectively evaluate physical function since the six-minute walk test is the only physical performance-based instrument routinely used to evaluated patients with SCD. It does not fully capture the various aspects of a patient's functional capabilities and impairments. Maintaining mobility is important to patients and it is important to evaluate this and detect changes early. In addition, many of the Supplemental and Exploratory measures will need to be validated in patients with SCD.

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Summary Table:

Domain/Subdomain	CRF	Classification	Notes
Assessments and Examinations/Acute Conditions	Acute Chest Syndrome	Varies	Containing Core elements: Temperature, Oxygen Saturation, Heart Rate, PaO2 value, Leukocytes Percentage Value, Hemoglobin Lab Value, Imaging (unless pregnant), Severity (Hospitalization, ICU, Ventilation)
Outcomes/Functional Cardiopulmonary	6 Minute Walk Test https://www.phenxtoolkit.org/protocols/view/90602	Core	Six-Minute Walk Test (6MWT) With Borg dyspnea scale Use change in absolute 6MW distance. Compare to healthy normative values based on age and gender.
Assessments and Examinations/ Lung Disease	Pulmonary Function Test	Core	Cooperative Study on Sickle Cell Disease (CSSCD) Pulmonary Function Testing Form
Assessments and Examinations/Renal	Renal Function Assessments	Varies	Containing Core elements: Sex, Race, Height, BMI, Serum Creatinine, Serum Cystatin C, Estimated GFR, Urine Albumin/Creatinine, Daily Urine Output, Systolic and Diastolic Blood Pressure)
Assessment and Examinations / Non-Imaging Diagnostics	Echocardiogram	Varies	Containing Core Elements: *Date of Birth, Date, Sex,* Height, Weight, Body Mass Index, Body Surface Area, Systolic and Diastolic Blood Pressure, Heart Rate, LV Septum, Posterior wall, LV end diastolic dimension, LV end systolic dimension, LV mass, LV end diastolic volume, LV end systolic volume, EF Simpson's (or EF visual estimate), Fractional shortening (Pediatric only), Global Longitudinal Strain, LVOT diameter, LVOT Peak

Domain/Subdomain	CRF	Classification	Notes
			Velocity and Velocity Time Integral, HR during LVOT VTI, AV Peak Velocity, AV Peak Gradient, LA Diameter, LA volume, RV Basal Diameter, RV Dilation, Tricuspid Annular Plane Systolic Excursion, RV Dysfunction, RA volume, IVC diameter, Estimated RA pressure, Tricuspid regurgitation peak velocity, Estimated RV systolic pressure, Mitral inflow peak E velocity, Mitral inflow peak A velocity, Septal e' velocity, Lateral e' velocity, Mitral regurgitation, Aortic regurgitation, Tricuspid regurgitation, Pulmonic regurgitation, Additional notes on valves (if any)
Assessments and Examinations/Imaging	Cardiac MRI	Varies	Containing Core Elements: *Date of Birth, Date, Sex,* Height, Weight, Body Mass Index, Body Surface Area, Systolic and Diastolic Blood Pressure, Heart Rate, Type of Scanner, Strength of Magnet, Contrast, Complications, LV size, LV hypertrophy, LV Global and Regional Function, LV late gadolinium enhancement, RV size, RV hypertrophy, RV global and regional function, LA size, RA size, LV Ejection Fraction, LV End-Diastolic Volume, LV End-Systolic Volume, LV Stroke Volume, Cardiac Output, LV End-Diastolic Mass, Left Atrium Diameter, LA Volume, Pulmonary artery, RV Ejection Fraction, RV End-Diastolic Volume, RV End-Systolic

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Domain/Subdomain	CRF	Classification	Notes
			Volume, RV Stroke Volume, Aortic valve annulus, Sinuses of Valsalve, Sinotubular junction, Ascending and descending aorta, LAD Territory segments, RCA Territory segments, Circumflex Territory segments, T2 Heart, T2 Liver
Assessments and Examinations/Imaging	Brain MRI -Silent Cerebral Infarct	Varies	Containing Core Elements: Adjudication Committee, MRI Type, MRI Silent Cerebral Infarct (SCI) Reading by 3 or more neuroradiologists, Location of SCI. Liem RI, Liu J, Gordon MO, Vendt BA, McKinstry RC 3rd, Kraut MA, Strouse JJ, Ball WS, DeBaun MR. Reproducibility of detecting silent cerebral infarcts in pediatric sickle cell anemia. J Child Neurol. 2014 Dec;29(12):1685-91. doi: 10.1177/0883073813506491. Epub 2013 Dec 5. PMID: 24309240; PMCID: PMC4096057.
Assessments and Examinations/Laboratory	Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP)	Supplemental-Highly-Recommended	Serum biomarker used in screening for pulmonary hypertension
Assessments and Examination/ Lung Disease	Pulmonary Hypertension	Supplemental-Highly Recommended	
Lung Disease Outcomes	Medical Outcomes Study SF-36 The original SF-36 (i.e., SF-36 v1) is freely available in public domain:	Supplemental	8 health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social

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Domain/Subdomain	CRF	Classification	Notes
	36-Item Short Form Survey from the RAND Medical Outcomes Study		functioning, energy/fatigue, and general health perceptions. See link to SF-36 Manual: https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html
Lung Disease Outcomes	PROMIS Item Bank v1.0 Dyspnea Functional Limitations https://www.healthmeasures.net/explore-measurement-systems/promis	Supplemental	Assesses the impact of dyspnea on ability to function while performing specific daily activities rated in terms of degree of difficulty while engaging in the activity over the past 7 days. Recommend to use response pattern scoring in HealthMeasures Scoring Service Yount SE, Choi SW, Victorson D, et al. Brief, valid measures of dyspnea and related functional limitations in chronic obstructive pulmonary disease (COPD). Value Health. 2011;14(2):307-315. doi:10.1016/j.jval.2010.11.009
Lung Disease Outcomes	PROMIS Item Bank v1.0 – Dyspnea Severity	Supplemental	Assesses the severity of dyspnea experienced in response to various specific activities over the past 7 days. Yount SE, Atwood C, Donohue J, et al. Responsiveness of PROMIS® to change in chronic obstructive pulmonary disease. J Patient Rep Outcomes. 2019;3(1):65. Published 2019 Oct 29. doi:10.1186/s41687-019-0155-9
Outcomes/Functional Cardiopulmonary	Heart Rate Recovery (HRR) Recovery of	Exploratory	For HHR1, subtract HR at 1 minute after completion of

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Domain/Subdomain	CRF	Classification	Notes
	heart rate 1 minute and 2 minutes after completion of 6MWT		6MWT from HR immediately after completion of 6MWT. For HRR2. subtract HR 2 minute after 6MWT from HR immediately after of 6MWT. Alvarado AM, Ward KM, Muntz DS, Thompson AA, Rodeghier M, Fernhall B, Liem RI: Heart rate recovery is impaired after maximal exercise testing in children with sickle cell anemia. J Pediatr. 2015, 166(2):389-393.e381.
Assessments and Examinations / Physical Examination	NIH Stroke Scale	Supplemental-Highly Recommended	See CNS notes and summary See here for NIH Stroke Scale Training and Certification: American Heart Association Lifelong Learning
Assessments and Examinations / Physical Examination	Questionnaire for Verifying Stroke-Free Status	Supplemental	See informational document
Assessments and Examinations / Lung Function	Spirometry Overread form	Supplemental	From Sickle Cell Anemia (SAC) Study
Assessments and Examinations / Lung Function	Spirometry	Supplemental	From SAC Study (contact curescinfo@emmes.com for forms)
Assessments and Examinations / Lung Function	Pulmonary Checklist, Instructions and Methacholine Challenge Testing	NA	From SAC Study (contact curescinfo@emmes.com for forms)
Assessments and Examinations / Lung Function	Static Lung Volume	Supplemental	From SAC Study (contact curescinfo@emmes.com for forms)
Assessments and Examinations / Lung Function	Impulse Oscillometry	Supplemental	From SAC Study (contact curescinfo@emmes.com for forms)

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Assessments and Examinations / Lung Function	Online and Offline Exhaled Nitric Oxide Forms	Supplemental	From SAC Study (contact curescinfo@emmes.com for forms)
Assessments and Examinations / Cardiac Function	Exercise Testing (For a copy of this test, please email curescinfo@emmes.com)	Exploratory	Badawy SM, Payne AB, Rodeghier MJ, Liem RI. Exercise capacity and clinical outcomes in adults followed in the Cooperative Study of Sickle Cell Disease (CSSCD). Eur J Haematol. 2018 Oct;101(4):532-541. doi: 10.1111/ejh.13140. Epub 2018 Aug 31. PMID: 29999202; PMCID: PMC6546160.
Treatment and Intervention Data/Asthma	Asthma Outcomes	Supplemental	For Asthma related questions – Key questions for outcomes. This form goes is accompanied by the medication form.
Treatment and Intervention Data/Asthma	Asthma Outcomes List	Varies (see Asthma Outcomes table)	ISAAC Core Questionnaire 6-7 ISAAC Core Questionnaire 13-14 ATS-DLD 78 CAMP Asthma Symptom Questionnaire TRACK (Test for Respiratory and Asthma Control in Kids) Childhood asthma control test (C-ACT) Asthma Control Test (ACT) Pediatric Asthma Quality of Life (PAQLQ) Asthma Quality of Life 12+ (AQLQ 12+) Asthma Quality of Life >17 (AQLQ) Peds QL Asthma Short Form (Contact us for copies of these forms curescinfo@emmes.com)
Treatment and Intervention Data/Asthma	Asthma Medications	Supplemental	

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Domain/Subdomain	CRF	Classification	Notes
Treatment and Intervention Data/Asthma	**Asthma Medications List**	**NA**	**Form based on SAC II Asthma medication CRF**

References: Ann T. Farrell, Julie Panepinto, Ankit A. Desai, Adetola A. Kassim, Jeffrey Lebensburger, Mark C. Walters, Daniel E. Bauer, Rae M. Blaylark, Donna M. DiMichele, Mark T. Gladwin, Nancy S. Green, Kathryn Hassell, Gregory J. Kato, Elizabeth S. Klings, Donald B. Kohn, Lakshmanan Krishnamurti, Jane Little, Julie Makani, Punam Malik, Patrick T. McGann, Caterina Minniti, Claudia R. Morris, Isaac Odame, Patricia Ann Oneal, Rosanna Setse, Poornima Sharma, Shalini Shenoy; End points for sickle cell disease clinical trials: renal and cardiopulmonary, cure, and low-resource settings. *Blood Adv* 2019; 3 (23): 4002–4020. doi: https://doi.org/10.1182/bloodadvances.2019000883