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**CureSCi CDE Project**
**Cerebrovascular Subgroup Summary**

Overall goal is to provide the key elements needed for standard data collection across various studies. If a study's focus is cerebrovascular assessments, the following recommendations have been made by this subgroup of the Cardiopulmonary, Renal and Cerebrovascular Working Group (WG). Many of the related elements for CNS are captured in already recommended CDEs. In order to not be redundant to other efforts, the summary of the outline for this subgroup is provided below. The other related form is the Silent Cerebral Infarct CRF with imaging adjudication recommendations with minimum elements to be collected. The cognitive assessments are also referenced below which is in collaboration with Outcomes WG.

The following measures are standard for assessment of neurological morbidity as a clinical outcome:
Demographics: Relative to cognitive function i.e. education, income
History: Neurology history –Development, symptoms, duration, rehab, impact on ADL, therapeutic interventions, medications, family history
Physical Exam: Neurology focused i.e. dysmorphic features, cranial nerves, muscle mass, strength, tone, DTR, movements, cerebellar function, sensory function
Imaging:

Standard
US: TCD (transcranial doppler, carotid)
MRI
MRA

Other
MRV
CT
CT angiogram
Conventional cerebral angiogram
Hemodynamic measures such as cerebral blood flow, oxygen extraction fraction and cerebrovascular reactivity
EEG

Non-imaging:

Battery cognitive assessments (see below)

Surveillance: History, PE, imaging, cognitive assessments
**Adjudication:**

**Neuroradiology**
**Neurology**

Comprehensive Assessments – diagnosis

- Infarctions- silent, ischemic, hemorrhagic
- Moya-moya
- Intracranial Stenosis
- Intracranial Aneurysm
- Intracranial Hemorrhage
- Seizure

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Cognitive Assessments:

| Domain | Subdomain | Population | Instrument Name | Classification | Notes |
|---|---|---|---|---|---|
| Cognitive | Global | 0-3.5 years | Bayley-III | Supplemental | Should global cognition and development be a focus of the study for infants, this would be preferred. |
| Cognitive | Global | 2.5-7 & 7/12 | 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 |
| Cognitive | Global | 6-16 & 11/12 | 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 |
| Cognitive | Global | Adults | 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 |
| Cognitive | Global | 3-6, 1-17, and 18+ Depending on Battery | NIH Toolbox[1] | 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). |

[1] NIH toolbox **NIH Toolbox administration guidelines during COVID-19 and social distancing** https://nihtoolbox.force.com/s/article/Coronavirus-Covid-19

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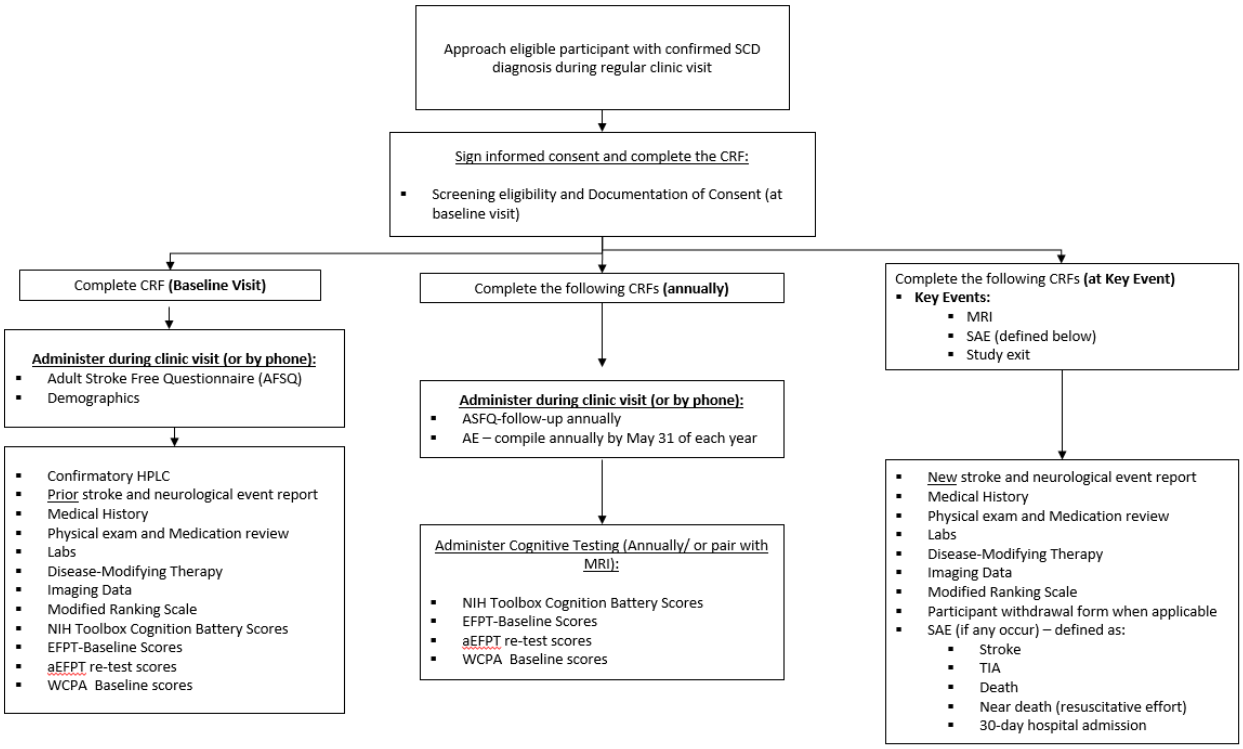
| Domain | Subdomain | Population | Instrument Name | Classification | Notes |
|---|---|---|---|---|---|
| Cognitive | Executive Functioning (and Attention) | Versions for 3-7, 8-11, and 12+ | NIH Toolbox: Flanker Inhibitory Control and Attention Test | Supplemental, Highly Recommended | NIH Toolbox measures generally preferred over other similar measures due to low participant burden and minimal resource requirements, as well as broad age ranges. |
| Cognitive | 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. |
| Cognitive | Executive Function | 9 and up | Trails A and B / TMT A | Supplemental | |
| Cognitive | Executive Function | 8-89 years | D-KEFS | Supplemental | |
| Cognitive | Executive Function | 6 years, 5 months to 89 | Wisconsin Card Sort Test | Supplemental | |
| Cognitive | 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. |
| Cognitive | Processing Speed | Adults | Processing Speed Index (of WAIS-III) | Supplemental | |
| Cognitive | 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. |

**Summary recommendations includes:**

- **MRA/MRI Definitions of Silent Cerebral Infarcts**
- **Cognitive Assessments (see above)**

**Sample Study Flowchart** [2]




A. Definitions for neurologic sequelae are derived from 2020 ASH CNS guidelines[1] that includes definitions from American Heart Association/American Stroke Association (AHA/ASA), World Health Organization (WHO) and excerpts from a 2019 Blood Advances publication on endpoints for sickle cell trials.[2]

CNS-related Excerpts from Blood Advances publication on endpoints for sickle cell trials. (Blood Adv 2019; 3 (23): 3982–4001)[i]:

[2] EFPT executive function performance testing
WCPA – weekly calendar planning activity
WCPA – weekly calendar planning activity
ASFQ – Similar to Questionnaire for Verifying Stroke-free Status (QVSFS)

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1. **Silent Cerebral Infarct definition[2]**: "Of note, the definition of an SCI is based on work by DeBaun and colleagues in the Silent Infarct Transfusion Trial: an infarct-like lesion was defined as an MRI signal abnormality that was at least 3 mm in 1 dimension and that was visible in 2 planes on fluid-attenuated inversion recovery (FLAIR) T2-weighted images, as determined by agreement of 2 of the 3 study neuroradiologists. The members of a neurology committee adjudicated a lesion as an SCI if the study participant had either a normal neurologic examination or an abnormality on examination that could not be explained by the location of the brain lesion or lesions. An enlarged SCI was defined as a previously identified SCI that increased by at least 3 mm along any linear dimension in any plane on MRI. In clinical trials, an adjudication process is needed to objectively confirm neurologic and imaging findings. As is the standard in all National Institutes of Health stroke trials, an adjudication committee is needed to objectively confirm neurologic and CNS-imaging findings. In the Silent Cerebral Infarct Multi-Center Clinical Trial, ~7% of all children believed to have SCI actually had strokes when evaluated by a local pediatric neurologist and later reviewed by a panel of pediatric neurologists."

2. **For stroke/ischemia as mentioned in ASH CNS guidelines[1]:**

   "In 2013, the American Heart Association/American Stroke Association (AHA/ASA) for the first time endorsed a definition of stroke that includes silent cerebral infarctions and silent cerebral hemorrhages typically identified by MRI of the brain. This change in definition reflects a shift in emphasis toward a radiological demonstration (tissue-based definition) of infarction or hemorrhage because permanent neurological injury may occur despite symptoms resolving in <24 hours. For patients with cerebral ischemia, the AHA/ASA stated that treatment should address the cause of the ischemic event and not be governed only by whether infarction has developed (in the case of TIA) or the size of the infarct.

   The traditional definition of stroke endorsed by the World Health Organization (WHO) requires clinical symptoms for >24 hours and has been in use since the 1970s. Our panel

affirmed the importance of silent cerebral infarcts given the known impact on cognition and an established biomarker for infarct recurrence in children and adults with HbSS or HbSβ$^0$ thalassemia and in the general population. However, we recognize that the MRI-based definition is challenging in low-middle–income settings where MRI is not widely available. Hence, the WHO definition of stroke is clinically relevant and generalizable to individuals living in both low-middle– and high-income settings."

3. **For abnormal TCD[1]:**

"The suggested threshold for treatment should be based on TAMMV (not peak systolic velocity) and, using non-imaging TCD techniques, is TAMMV ≥200 cm/s whereas for imaging the equivalent is time-averaged mean maximum velocity ≥185 cm/s. Abnormal TCD is defined as 2 TCD measurements >200 cm/s or a single measure of >220 cm/s using the non-imaging technique, and 2 >185 cm/sec or 1 >205 cm/s using the imaging technique."

Additional anatomic measures and brain MRI techniques to consider are listed as either recommended assessments (Table 3) or non-standard assessments that would enhance the brain evaluation (Table 4 ).
https://ashpublications.org/bloodadvances/article/3/23/3982/429244/End-points-for-sickle-cell-disease-clinical-trials)

**Table 3. Recommended anatomic measures for MRI of brain in SCD**

| 3 Tesla MRI method: anatomical (basic) | Outcome measure | Rationale | Duration, min |
|---|---|---|---|
| 2D T2w FLAIR (2 planes: axial and coronal) or 3D T2w FLAIR (reconstructed to 3 orthogonal planes) | 1. Infarct (count)<br>2. White matter lesion (count)<br>3. Alternative pathology (Dx) | Evaluate presence of prior and new overt strokes or silent cerebral and cerebellar infarcts (SCIs); prior SCI is a risk factor for future SCI | 5-7 (cumulative) |
| 3D T1w MPRAGE | 1. Infarct (count)<br>2. Tissue volume (volume; mm$^3$) | Required with FLAIR to characterize infarct (FLAIR hyperintense, T1 hypointense); progressive tissue atrophy may be associated with cognitive decline | 5 |
| 2D T2w | 1. Infarct (count)<br>2. Lesion (count) | Adds clarity for temporal lobe lesion identification | 3 |

An adjudication committee is strongly recommended for imaging outcomes.
2D, 2-dimensional; Dx, diagnosis; MPRAGE, Magnetization Prepared–RApid Gradient Echo.

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**Table 4. Additional MRI measures of brain in SCD requiring further research as potential end points in clinical trials**

| 3 Tesla MRI method | Outcome measure | Rationale | Duration, min |
|---|---|---|---|
| Head time-of-flight magnetic resonance angiography | 1. Vasculopathy (percent; categorical)<br>2. Associated pathology (eg, moya-moya) | Noninvasive alternative to head CTA/DSA; categorical grading (use 0-4)[205] | 5 |
| Neck time-of-flight magnetic resonance angiography | 1. Vasculopathy (percent; categorical) | Noninvasive alternative to neck CTA; presence of cervical vasculopathy extent remains debated in SCD | 6 |
| Diffusion tensor imaging | 1. White matter structural connectivity<br>2. Tract-based spatial statistics<br>3. Fractional anisotropy, mean diffusivity, etc | Fiber tracking and related parameters (anisotropy, diffusivity) may indicate white matter damage and describe symptomatology | 6 |
| Susceptibility weighted imaging | 1. Microbleeds (count; volume)<br>2. Quantitative susceptibility (iron)<br>3. Venous density | Characterize microvascular disease and iron deposition | 4 |
| Diffusion-weighted imaging if acute CNS event | 1. Acute infarct (count) | Inform presence of recent infarcts | 1 |
| MR venography if acute CNS event | Thrombosis, stenosis | Unlikely to be abnormal in asymptomatic | |
| **Hemometabolic** | | | |
| Arterial spin labeling | 1. Regional cerebral blood flow (mL/100g/min) | Inform extent of hypo- or hyperperfusion; hypoperfusion indicative of tissue-level impairment from vasculopathy; hyperperfusion marker of how well parenchyma is responding to anemia and reduced blood delivery; may also provide indicator of arterial-venous shunting | 4 |
| T2-relaxation-under-spin-tagging | 1. OEF (ratio of oxygen consumed to oxygen delivered)<br>2. $CMRO_2$; mL $O_2$/100 g/min; requires CBF measurement | Inform extent to which total oxygen delivery is meeting requirements; elevated OEF may be indicator of new or recurrent infarct; reduced $CMRO_2$ may indicate suppressed neuronal activity and new lesion risk | 2 |
| Phase contrast angiography (head and neck) | 1. Quantitative velocity assessment of major intracranial (eg, first segment MCA) and cervical vessels (ICA, BA) (mm/s) | Allows for whole-brain CBF assessment (with tissue volume information), which is not possible with arterial spin labeling; evaluate elevated flow velocity (provide comparison for TCD) | |
| Blood oxygenation level-dependent or arterial spin labeling cerebrovascular reactivity (requires respiratory stimulus such as hypercapnic or IV/oral vasodilatory stimulus such as acetazolamide) | 1. Cerebrovascular reactivity, an indicator of microvascular reserve capacity (signal change) | Cerebrovascular reserve will be exhausted when CBF can no longer increase to compensate for anemia and/or vasculopathy | 8 |

An adjudication committee is strongly recommended for imaging outcomes. Vasculopathy is a surrogate marker and difficult to measure as an outcome.
BA, basilar artery; CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate of $O_2$ consumption; CTA, computed tomographic angiography; DSA, digital subtraction angiography; MR, magnetic resonance; OEF, oxygen extraction fraction.

**Additionally, the article states (quoted below Farrell AT et al):**

B. Based on previous studies, the brain panel also recommends that the following 3 types of measures be completed for meaningful interpretation of cognition:

1. A measure of the home or social environment, such as the Home Observation for Measurement of the Environment (HOME), a semi-structured interview and observation tool for assessing parent-child interaction as well as the quantity and quality of stimuli present in the home environment. The HOME has been shown to be a reliable tool that can screen for developmental delay and is predictive of later academic achievement.
2. The head of household's level of educational attainment, which is also significantly related to a child's cognition.
3. Recording of average daily morphine equivalent dose, based on a meta-analysis that found association of deficits with chronic opioid use, to include verbal working memory, cognitive impulsivity (risk-taking), and cognitive flexibility (verbal fluency).

C. Further the brain panel recommended (quoted below Farrell AT, et al):

**Educational attainment**

A child's primary occupation is to attend school. Complications from SCD result in children missing, on average, 15 to 22 days of school per year. New therapies could be considered successful if children were able to attend more school days. For adults, the process of attending more days of work would also be a positive change. Higher levels of educational attainment are associated with better health and greater wealth. The brain panel recommends that the following questions be asked to assess short-term benefit over the course of 1 school year:
For missed school days, how many were due to (a) scheduled (medical appointments) and (b) unpredictable hospitalizations?
For a longer-term study, the following example questions have been used in BABY HUG and the Silent Cerebral Infarct Transfusion (SIT) trial to assess educational outcomes in the United States:

a. What is your child's current grade?
b. Has your child ever been held back or repeated a grade?
    i. If yes, how many grades? (1, 2, 3, or more)
c. Does your child have any accommodations because of learning differences?
d. Check all that apply
    i. Special Education Services
    ii. 504 plan
    iii. IEP-individualized education plan
    iv. Special tutoring or classes not available to regular students
    v. Other
        1. Describe: _____
    vi. My child does not receive any accommodation for learning differences

As a measure of educational attainment for adolescents and adults, questions can be asked about highest-grade level completed, graduation status from high school, and dropout from high school. These measures would be used to assess changes over at least 1 year to balance the variation in seasons of weather and longer-term benefit. With global studies, regional differences in educational systems will necessitate different measures of educational attainment.

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**1.** M. R. DeBaun, L. C. Jordan, A. A. King, J. Schatz, E. Vichinsky, C. K. Fox, R. C. McKinstry, P. Telfer, M. A. Kraut, L. Daraz, F. J. Kirkham, M. H. Murad; American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease

in children and adults. *Blood Adv* 2020; 4 (8): 1554–1588.
doi: https://doi.org/10.1182/bloodadvances.2019001142
**https://ashpublications.org/bloodadvances/article/4/8/1554/454384/American-Society-of-Hematology-2020-guidelines-for cerebrovascular disease**

2. Ann T. Farrell, Julie Panepinto, C. Patrick Carroll, Deepika S. Darbari, Ankit A. Desai, Allison A. King, Robert J. Adams, Tabitha D. Barber, Amanda M. Brandow, Michael R. DeBaun, Manus J. Donahue, Kalpna Gupta, Jane S. Hankins, Michelle Kameka, Fenella J. Kirkham, Harvey Luksenburg, Shirley Miller, Patricia Ann Oneal, David C. Rees, Rosanna Setse, Vivien A. Sheehan, John Strouse, Cheryl L. Stucky, Ellen M. Werner, John C. Wood, William T. Zempsky; End points for sickle cell disease clinical trials: patient-reported outcomes, pain, and the brain. *Blood Adv* 2019; 3 (23): 3982–4001.
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