

**NINDS CDE Project**  
**Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)**  
**Neurologic/Cognitive/CNS Imaging Subgroup**

We first split the overall Neurologic/Cognitive/CNS Imaging Subgroup into three sections as each of them has large distinct, yet overlapping areas of expertise that need to be tapped into when considering selection of appropriate assessment tools/instruments. Each subgroup selected a chair responsible for timely selection and review of instruments. The perspectives of clinicians, researchers, and patient advocates were included in the development of these recommendations. As in the other subgroups, patient advocates participated alongside investigators and clinicians and commented on the documents being created.

**Neurologic**

The Neurologic subgroup developed a Neurological Exam case report form (CRF) modelled on the neurological exam used in the Centers for Disease Control and Prevention's (CDC's) longitudinal "Multi-site Clinical Assessment of ME/CFS (MCAM)". The cerebellar and reflex examinations were expanded based on subgroup clinician and patient advocate feedback. The Neurological Exam CRF is appropriate for use in all ME/CFS subpopulations, including both adult and pediatric populations. Age/Date of Birth should be noted on the CRF. The data elements on the Neurological Exam CRF have classifications of Supplemental-Highly Recommended, Supplemental and Exploratory. The Supplemental-Highly Recommended data elements are gait assessment and Military and Tandem Romberg tests.

The burden of completing a thorough neurologic exam was considered within the context of a typical overall study burden. The thorough neurologic exam was not considered to be excessively long. However, study personnel need to be sensitive to the impact of cognitive/physical exertion on ME/CFS study participants.

No issues concerning the recommended neurological exam should be encountered when administered to ME/CFS study participants as it is already used within that context by the CDC. Issues specific to ME/CFS were addressed by adding a more detailed cerebellar and reflex exam section to the protocol. The subgroup feels that the CRF, along with the neurological exam protocol will adequately address and identify the neurological profile of study participants with ME/CFS.

**Cognitive**

The Cognitive subgroup used the following approach for selection and classification of instruments:

First, the cognitive subgroup received a list of neuropsychological assessment tools that were made available by NINDS CDE that have been selected as CDEs for other disease categories across various cognitive domains.

Second, the subgroup identified a list of cognitive domains that need to be considered in order to tap into areas of cognitive strengths and weaknesses pertinent to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) based on previously published research. The group identified the following areas of cognitive subdomains for consideration: Demographic Information, Intellectual

Ability/Premorbid Function/Academic Skills, Visual and Auditory Attention/Information Processing/Working Memory, Visual and Auditory Learning and Memory, Executive Function, Receptive and Expressive Language Function, Motor Function, Visual Perception, Validity Testing/Motivation, Emotional/Behavioral Function, and Quality of Life Assessments.

Third, in addition to the list of neuropsychological assessment tools provided by NINDS CDE, the subgroup added neuropsychological measures that had previously been used in ME/CFS in general as well as in studies examining cognitive aspects of ME/CFS specifically. As the number of cognitive studies in ME/CFS has decreased over the past decade, subgroup members were also encouraged to submit neuropsychological tools that they knew had been successfully used in clinical practice as well as measures that were currently used in ongoing studies. All assessment tools submitted were then cataloged according to the cognitive subdomains identified. At this point, we had collected 57 measures that had been previously used either in research or clinically for neuropsychological and behavioral assessment in adults with ME/CFS and 37 measures for evaluation of the pediatric ME/CFS population.

Fourth, subgroup members volunteered to review and classify collected instruments based on their appropriateness of use in adult and pediatric ME/CFS populations, frequency of use in research studies, ease of administration and degree of patient burden to complete the evaluation tool based on research and clinical experience, best fit for cognitive subdomain, normative data available, and applicable age range.

Finally, 15 assessment tools were identified as CDE candidates for an adult ME/CFS population, 5 as specific for a pediatric ME/CFS population, and 10 as covering the pediatric and adult age range. Those that had been used in at least 2 ME/CFS studies, are covering areas of cognition identified as problematic in ME/CFS, and those instruments that are frequently used clinically in these areas were classified as Supplemental-Highly Recommended. Assessment measures evaluating downstream effects of primary cognitive deficits as well as those providing supplementary information were classified as Supplemental. Those tools that have been used sporadically in published studies and/or clinically were classified as Exploratory. Some neuropsychological tools suggested to be included as CDEs were only normed for adult or pediatric populations. Many of the better-known instruments provided norms across the age range. See Supplemental-Highly Recommended Instruments in table below.

Computer administration of neuropsychological assessment tools is becoming more and more common, but can pose an issue for the ME/CFS population due to significant challenges in information processing/multi-tasking (remembering the task demands in addition to which buttons to push). Also, some individuals in this disease group are photosensitive and thus have difficulties looking at a computer screen for extended periods of time. Additionally, time to complete instruments/forms can be an issue for many patients because of scant cognitive/physical energy.

Especially for research purposes, brief screening/evaluation batteries are coming more and more to the forefront and tend to be the preferred means for data collection due to time constraints. However, cognitive deficits identified in ME/CFS benefit from either extended administration time or increased task complexity (i.e., challenging information processing/working memory tasks) to elucidate the issues associated with ME/CFS. The recommendation for cognitive measures, as with all the CDEs, are for clinical research studies. If there are questions of patient safety, testing will be discontinued. The goal of the cognitive testing is to test the patient limit and this will be in the informed consent. These

measures must be given by trained personal. We do have to test to where the deficit lies but the person needs to be licensed practitioner.

The subgroup considered the inclusion of the pediatric ME/CFS population as well as bed bound patients. Extensive consideration was given to the burden and/or acceptability of instruments to people with ME/CFS as it is of prime importance. The subgroup was able to make recommendations that capture the diversity and complexity of the clinical presentations of ME/CFS and identify a set of cognitive tools that should be used as primary assessment tools to reduce the heterogeneity of ME/CFS cognitive studies.

The process employed to identify appropriate CDEs for this disease group identified a reasonable selection of tools that can be used to achieve interpretable, valid and reliable endpoints in research studies. The subgroup feels that the unmet need really is that investigators in previous studies of cognitive function in ME/CFS used a multitude of evaluation tools that makes it difficult to compare and contrast study results. Our hope is that our work on this committee will ameliorate this deficiency.

### **CNS Imaging**

The CNS Imaging subgroup used the following approach for selection and classification of data elements: The basic case report forms were obtained from already-existing neuroimaging resources maintained by the NINDS CDE Project. Minor modifications were made to the forms to make them optimal for use in ME/CFS studies. Additionally, two new CRFs for Low-Resolution Electromagnetic Tomography (LORETA) and Quantitative Electroencephalography (qEEG) were developed. The subgroup attempted to include all neuroimaging modalities that have been used in more than one ME/CFS study in the past 5 years. All of the data elements are classified as Supplemental-Highly Recommended based on the neuroimaging modality being used in a study. For example, if a study is using Diffusion Tensor Imaging (DTI), all of the data elements included in the DTI CRF should be collected.

The recommendations for this subgroup include the following Case Report Forms (CRFs):

- Diffusion Tensor Imaging (DTI)
- Electroencephalography (EEG)
- Functional Magnetic Resonance Imaging (fMRI)
- Low-Resolution Electromagnetic Tomography (LORETA)
- Magnetic Resonance Imaging (MRI)
- Magnetic Resonance Spectroscopy (MRS)
- Magnetoencephalography (MEG)
- Positron Emission Tomography (PET)
- Quantitative Electroencephalography (qEEG)

The selected case report forms are appropriate for use in all ME/CFS subpopulations who are eligible for neuroimaging protocols, including both adult and pediatric populations. The forms will not need to be modified for pediatric participants.

Additionally, the subgroup developed guidelines for Functional Imaging Tasks and Parameters using standard protocols from the Human Connectome Project and other multi-site neuroimaging initiatives.

Participant fatigability and exhaustion were of utmost concern. Guidelines were adopted specific to ME/CFS neuroimaging studies to address this concern. Much discussion centered on typical duration of imaging studies and the burden on ME/CFS participants. These issues were addressed in a guidance document targeted to neuroimaging studies in ME/CFS.

There are no special considerations for the neuroimaging of ME/CFS individuals above and beyond general guidelines for working with participants with chronic pain, fatigue, and other conditions. Neuroimaging data collection using the outlined tools should be as valid as in any other condition. Interpretation and generalizability of ME/CFS neuroimaging data may, however, be limited by the inability to get severely affected individuals to the scanner.

The subgroup is confident they were able to address the current state of neuroimaging in ME/CFS and provide the tools that would be valid for several years. Because neuroimaging is a rapidly-developing field, changes will likely need to be made to these documents to reflect new advances and standards.

Table 1. Cognitive Instruments Supplement-Highly Recommended

| Instrument Name   | Adult and/or Pediatric | Classification (Core, Supplemental-Highly Recommended, Supplemental, or Exploratory) |
|---|------------------------|--|
| Word Reading Subtest of the Wide Range Achievement Test (WRAT-4)  | Adult and Pediatric    | Supplemental-Highly Recommended  |
| Paced Auditory Serial Addition Test (PASAT)   | Adult                  | Supplemental-Highly Recommended  |
| Stroop Test   | Adult and Pediatric    | Supplemental-Highly Recommended  |
| Children's Paced Auditory Serial Addition Task (ChiPASAT)   | Pediatric              | Supplemental-Highly Recommended  |
| Beck Anxiety Inventory (BAI)  | Adult                  | Supplemental-Highly Recommended  |
| Beck Depression Inventory II (BDI-II)   | Adult and Pediatric    | Supplemental-Highly Recommended  |
| Delis-Kaplan Executive Function System (D-KEFS) Recommended modules: Color-Word-Interference Test -- , Trail Making Test -- , Verbal Fluency -- | Adult                  | Supplemental-Highly Recommended  |
| Edinburgh Handedness Inventory  | Adult                  | Supplemental-Highly Recommended  |
| California Verbal Learning Test - Second Edition (CVLT-II)  | Adult                  | Supplemental - Highly Recommended  |
| California Verbal Learning Test - Children (CVLT-C)   | Pediatric              | Supplemental - Highly Recommended  |
| Rey-Osterrieth Complex Figure Test (ROCF)   | Adult and Pediatric    | Supplemental-Highly Recommended  |