NINDS CDE Project
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)
Fatigue Subgroup

The fatigue subgroup started by discussing the types of fatigue and agreed to general fatigue, physical fatigue, mental fatigue (cognitive difficulties), post-exertional fatigue, and fluctuating fatigue. The subgroup agreed that some of the types of fatigue could overlap with other domains and that the types need to be further defined and rationalized against these other domains. The subgroup also discussed the different ways in which fatigue instruments have been used, including to assess severity, functional impact, and treatment outcomes, and also in diagnosis (at least in differentiating ME/CFS from depression). Further evaluation is needed to clarify the intended range of uses of the fatigue instruments.

The subgroup considered the list of existing fatigue instruments and CRF questions that were suggested by working group members as having utility in ME/CFS clinical care and research and also those from other NINDS CDE Disease recommendations. The subgroup selected measures from this list for further review. Members reviewed each existing instrument as they are currently being used in ME/CFS and identified the appropriate classification for them. The reviews included whether the measures had been used in ME/CFS research, the advantages and limitations for use in ME/CFS research, psychometric properties, availability, and whether the validation relied on Oxford or Reeves definition cohorts, as these are now considered inappropriate for use in ME/CFS. The subgroup considered whether the instruments addressed the different types of fatigue, the range of severity seen in ME/CFS, and also the sensitivity of the instrument to capture worsening. Consensus was reached through subgroup teleconference discussions and resulted in a recommendation for the appropriate classification for them. A patient and a patient advocate were involved at the start and at the end of subgroup deliberations and were able to provide input on the patient experience of fatigue. Additional patient involvement will be essential in future initiatives to clarify this important symptom and identify the best tools to assess it.

The instrument and CRF recommendations from the Fatigue Subgroup are shown in the table below. The recommendations for this subgroup include measures which are applicable to both the adult and pediatric populations. The instruments are generally short and easy to use. Because of ceiling and floor effects, some instruments may be limited in their use for distinguishing severity levels among patients and in assessing change due to treatment or to exertion.

Currently, there is a long list of instruments used to assess fatigue, each with advantages and disadvantages. Unfortunately, there is not a single encompassing instrument that measures all facets of fatigue across the range of severity with the needed sensitivity. Further, while a core instrument is needed to assess fatigue as a case defining criteria, we have not made a recommendation for such an instrument at this time.

As discussed further below, additional research is required to clarify the fatigue types and the alignment with other domains and also clarify the required uses of these instruments. Given the potential need for multiple instruments, one option to achieve a common fatigue measure is by harmonizing these instruments in such a way that enables reporting fatigue on a common metric.

Both PROMIS and Neuro-QoL Fatigue measures are drawn from item response theory – calibrated item banks. This fact enables use of a linking procedure referred to as PROsetta Stone. After co-administration of any of the questionnaires below with a sufficient number of PROMIS fatigue items, the two can be linked after confirming the assumption that they are measuring a common underlying trait (i.e., fatigue). This linking procedure produces a "crosswalk" that enables reporting fatigue on the PROMIS metric, regardless of what questionnaire was used to assess the patient. Looking at the content of the items (questions) in the instruments below, it became clear that there was extensive similarity in the content. The questions asked in one instrument are very similar to those questions asked in another. Yet, they are scored differently. The PROsetta Stone approach enables scoring on a common metric, which could then be regarded as the fatigue CDE. This work has moved beyond theoretical; PROMIS fatigue has been co-calibrated with (and therefore linked to) Neuro-QoL, the FACIT-Fatigue, and the SF-36 Vitality scale. Associated crosswalks have been published and are available at www.prosettastone.org. Through co-administration/co-calibration of PROMIS questions, there is the potential to link other fatigue instruments, including ones recommended below. Even though PROMIS fatigue is currently listed as Exploratory, the recommendation is also that it be used in conjunction with Fatigue Severity Scale so that its individual elements can be validated for this disease.

Reference: Lai JS, Cella D, Yanez B, Stone A. Linking Fatigue measures on a Common Reporting Metric. Journal of Pain and Symptom Management. 2014; 48(4): 639-648.

Issues discussed by this subgroup as well as other working group members include ceiling effects in ME/CFS of fatigue instruments, the lack of validation in ME/CFS, and questions about the ways in which the fatigue tools have been used in the past and should be used going forward. At least some of the existing tools have known ceiling effects and thus may not be able to cover the full range of severity seen in ME/CFS, including the change in fatigue as a result of exertion. For instance, fatigue tools have been used to discriminate fatigue from depression and other fatiguing conditions and to help distinguish when fatigue is caused by poor sleep hygiene rather than ME/CFS in children. But it is not clear how well a fatigue instrument can do that across all levels of severity of ME/CFS and the other conditions evaluated.

In a few instruments, reported thresholds for ME/CFS were based on studies using case definitions that have since been downgraded by the NIH Pathways to Prevention report or the 2015 Institute of Medicine report because those definitions could encompass patients with other conditions. Those instruments are both rated exploratory and a note added about the issue.

As with any symptom in ME/CFS, a challenge in assessing fatigue is the variability of symptom severity on good days and bad days and particularly as a result of the level of exertion prior to or during the study. Researchers will need to account for this in study design.

As mentioned above, the first priority is to further clarify the meaning of fatigue and define what the types of fatigue are and rationalize these against other domains. For instance, how is mental fatigue defined separate from the cognitive impairment that is part of the cognitive domain? And is post-exertional fatigue an aspect of fatigue or of PEM. In doing this, it will be important to validate this against the patient experience of PEM. This must be a patient-centered effort that starts with the patient experience of fatigue. Jason has published a paper subgrouping fatigue into 5 qualitative types that should be considered. (http://www.dsq-sds.org/article/view/938/1113)

The second need is to clarify the expected uses (e.g. case ascertainment, treatment outcome, severity, differentiation from other conditions, impact of fatigue, etc) that the fatigue instruments need to be able to perform. This can then be used to assess whether the experience of fatigue in ME/CFS requires disease- specific instruments to perform the different types of assessments of fatigue. Or alternatively, can a general-purpose instrument, such as PROMIS, be used for one or more of these different uses. The advantage of PROMIS is that it would allow comparison across diseases. This will require validating the patient experience of fatigue against the PROMIS item bank. Even if a disease-specific instrument is needed for certain uses, the PROMIS instrument could have significant utility for assessing aspects such as severity and treatment outcomes and has the advantage of being cross-linked with other measures.

The subgroup identified that there is still a need for a core instrument to be used across all studies to assess fatigue as a case defining criteria. In addition, and for future consideration, is need for instruments sensitive enough to assess fatigue across the full range of severity and as it changes due to either exertion or to treatment. As noted in the recommendation details, a number of the existing instruments have known ceiling effects when used in ME/CFS.

Recommendations Summary Table

Instrument / Scale / CRF Name *Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs*	**Population**	**Classification** (e.g., Core, Supplemental - Highly Recommended, Supplemental, Exploratory)	**Other Information, Instrument Use**
Fatigue Severity Scale (FSS)	Adult	Supplemental – Highly Recommended	Measure of the effect of fatigue on function
Checklist for Individual Strength - Fatigue (CIS)	Adult	Supplemental	Measures fatigue severity (subjective experience of fatigue); concentration problems (mental fatigue); reduced motivation and reduced activity level
Fatigue/Activity Record and Diary	Adult; Pediatric	Supplemental	Measures self-reported activity; can be correlated with physical activity monitors, biomarkers (e.g., cytokines) and PEM
Fatigue Visual Analog Scale	Adult; Pediatric	Supplemental	Measures fatigue severity but not designed to be used as a standalone assessment of fatigue severity and it should be administered with another measure
Wood Mental Fatigue Inventory	Adult; Pediatric	Supplemental	Measures General Fatigue, Sleep/rest problems, Cognitive fatigue
Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue	Adult	Supplemental	

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Pediatric Quality of Life Inventory, Multidimensional Fatigue Scale	Pediatric	Supplemental	Pediatric measure of effect of fatigue on quality of life
Patient-Reported Outcomes Measurement Information System (PROMIS) - Fatigue	Adult	Exploratory	Metric to potentially link other measures
Neuro QoL Adult Bank - Fatigue	Adult; Pediatric	Exploratory	Measures effect of fatigue on quality of life
Modified Fatigue Impact Scale (MFIS)	Adult	Exploratory	Measures the effect of fatigue on physical, cognitive and psychosocial functioning
Multidimensional Fatigue Inventory (MFI)	Adult	Exploratory	Measures general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity
Grip Strength Fatigue	Adult; Pediatric	Exploratory	Measure of fatigability