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

Sleep disturbances are experienced by over 90% of people affected by ME/CFS and consequently are included as part of the criteria for most ME/CFS case definitions. The most commonly reported symptom among ME/CFS patients is awakening unrefreshed, despite an adequate amount of uninterrupted sleep. This symptom may be associated with difficulties initiating or maintaining sleep; sleeping too much or too little; or sleeping during the day and being up at night. However, it is important to identify co-morbid sleep disorders, such as sleep apnea or restless leg syndrome, and to exclude narcolepsy as an alternative diagnosis.

Therefore, the Sleep Subgroup divided its tasks into the following components:

a. Developing a short assessment tool that would be useful for all ME/CFS studies designating the general sleep issues any individual study participant experiences.
b. Identifying instruments that screen for other sleep disorders when recruiting study participants. Studies have often not been explicit or have not used a standardized/ systematic method to assess for the presence of sleep disorders. It is important to identify whether the sleep disorder is a co-morbid condition potentially affecting study outcomes or is the primary explanation for putative ME/CFS symptoms, in which case a diagnosis of ME/CFS would not be appropriate.
c. Reviewing instruments for assessing the quality and quantity of sleep and its impact on function.
d. Developing a case report form for reporting common data elements for studies specifically focused on sleep.
e. Identifying instruments which can be used for assessing the most common sleep disturbance in ME/CFS, unrefreshing sleep. Recently, the sleep medicine field has come to recognize unrefreshing sleep as an important symptom, separate and independent of other sleep issues. This has special relevance for ME/CFS as some affected persons continue to experience unrefreshing sleep despite the occurrence of uninterrupted sleep.
f. Developing objective outcome measures related to sleep.

Criteria for selection and classification of instruments/ outcomes/ data elements include: relevance to ME/CFS, prior testing and/or use in ME/CFS or other medical conditions, psychometric characteristics, trial participant and researcher burden, and easy accessibility (e.g. copyright, cost, etc. issues).

We reviewed sleep issues related to children and adults but found no patient-reported outcome measures that were well-tested in children. As there is a dearth of reported studies of sleep disturbances in young people, standardized pediatric scales provide some descriptive information (for example, sleep hygiene) but were not validated for the ME/CFS population. They also fail to address the central issue of non-restorative sleep.

Instruments differed in their reporting timeframes, for example the DSQ required 'last 6 months' whereas the Pittsburgh, 1 month and others did not specify a timeframe. The purpose of the study and whether change is being assessed will need to consider this issue.

Subtypes within ME/CFS have not been clearly identified, therefore instruments and elements remain uniform to assess all subjects with this disease.

Below is a Summary Table of recommendations for the Sleep Subgroup

Instrument/CRF Name	Population	Classification	Purpose
Sleep Questions For All Studies	Adults; Pediatrics	Core (NHANES questions are Exploratory)	Assess for presence, frequency, and/or severity of sleep disturbances
Sleep - Focused Study Questionnaire	Adults; Pediatrics	Supplemental Highly-Recommended (One question is Supplemental)	Document characteristics of sleep-focused studies
Sleep Assessment Questionnaire – Moldofsky	Adults	Supplemental Highly-Recommended	Screen for primary and co-morbid sleep disorders; assess non-restorative sleep
Pittsburgh Sleep Quality Index (PSQI)	Adults; Pediatrics	Supplemental	9 item assessing sleep quality, latency, duration, disturbance, efficiency, daytime dysfunction during the last month
Stanford Sleepiness Scale (SSS)	Adults	Supplemental	Used for monitoring comorbid daytime sleepiness
Sleep Disorders Screening Checklist	Adults	Supplemental	Screen for primary and/or co-morbid sleep disorders
Holland Sleep Disorders Questionnaire (HSDQ)	Adults; Pediatrics	Supplemental	Screen for primary and/or co-morbid sleep disorders
Epworth Sleepiness Scale (ESS) - Children's Version	Pediatrics	Exploratory	Screen for daytime sleepiness
Nonrestorative Sleep Scale (NRSS)	Adults	Exploratory	Assess non-restorative sleep
Global Sleep Assessment Questionnaire (GSAQ)	Adults	Exploratory	Screen for primary and/or co-morbid sleep disorders
Restorative Sleep Questionnaire (RSQ)	Adults	Exploratory	Assess non-restorative sleep
Adolescent Sleep Hygiene Scale (ASHS)	Pediatrics	Exploratory	Screen for common sleep hygiene factors affecting sleep quality
Polysomnography (PSG) for ME/CFS	Adults; Pediatrics	Supplemental	

The Minimal Data Element for CFS research paper[1] suggested that: the frequency and severity of all symptoms be recorded; the Epworth Sleepiness Scale be regarded as an "essential" item; and that heart rate variability be classified as an "additional" item both under sympathetic activity and allostatic load.

Most of the study participant-reported instruments we recommend include taking into account the frequency of symptoms measures. We have also included nocturnal heart rate variability as a supplemental recommended objective outcome measure for studies focused on sleep.

We did not recommend the adult version of the Epworth Sleepiness Scale because the scope of the instrument was deemed to be too narrow, assessing only for daytime sleepiness and possible sleep apnea.

Only a few patient-reported outcome measures assessing sleep have been regularly used in ME/CFS. Many of these appear to be focused on assessing daytime sleepiness or to determine the presence of sleep apnea. In particular, virtually no studies have explored unrefreshing sleep in-depth despite this being the most common sleep symptom. This is at least partly due to the lack of recognition of unrefreshing sleep in the sleep field as an independent symptom until recently. Common data elements for sleep-focused studies were drawn from an analysis of ME/CFS sleep studies and a published review[2] of ME/CFS sleep studies that noted problems comparing study results due to the heterogeneity of studies.

It is important to note some of the unmet needs/unanswered questions identified via the CDE process. Future studies of sleep in ME/CFS Sleep need to:

a. Screen for sleep disorders among study subjects in an explicit, systematic way.
b. Cease assuming that complaints of sleep symptoms in ME/CFS are consistent within and between subjects; more research is needed on the specific types of sleep issues experienced, particularly unrefreshing sleep.
c. Stop grouping ME/CFS study participants who do not experience sleep problems together with those who do in studies and analyses; both the Fukuda and the ME – ICC do not require sleep dysfunction to qualify for them: consequently, for many prior sleep studies using Fukuda, it is not clear how many of the study subjects suffered from sleep issues. Moreover, participants who no longer experience sleep problems because of medications, supplements, behavioral measures, etc. should still be regarded as having sleep problems if they require treatment to sleep well. Our CRFs include items about treatment for sleep.
d. Focus on sleep issues in children and adolescents affected by ME/CFS. Even less is known about sleep issues in young people than adults.
e. Identify objective biomarker(s) associated with the sleep abnormalities observed in patients. To date, given prior caveats listed in this section, traditionally- administered and interpreted polysomnography sleep studies have not found any objective indices that are consistently abnormal in ME/CFS patients or which correlate with the symptoms patients express. There are

[1] Jason LA, Unger ER, Dimitrakoff JD, et al. Minimum data elements for research reports on CFS. Brain, behavior, and immunity. 2012;26(3):401-406. doi:10.1016/j.bbi.2012.01.014.

[2] Jackson ML, Bruck D. Sleep Abnormalities in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A Review. Journal of Clinical Sleep Medicine : JCSM : Official Publication of the American Academy of Sleep Medicine. 2012;8(6):719-728. doi:10.5664/jcsm.2276.

some promising studies on sleep transitions and heart rate variability which need to be replicated. Such research is greatly needed and should be encouraged.

f. Develop and validate a sleep questionnaire that is specific to patients with MECFS.
g. Query patients undergoing studies about agents they take to help their sleep, including not only prescription medications specifically approved for sleep (e.g. zolpidem) but also other medications, over-the-counter drugs, herbs, and supplements (e.g. gabapentin, low-dose naltrexone, antihistamines, valerian root). Timing of last dose should be considered as some agents require time to completely wash out of the body.

Questions about activities right before sleeping such as the time of latest food/beverage ingestion, amount of `texting' or `watching t.v.', etc. may be an issue. Diurnal variation in length and quality of sleep are common and should be accounted for in the appropriate sleep questionnaire administered to these subjects. These items could potentially be added to research questionnaires as supplemental items if not included on a validated instrument.

Input from Patient Advocates played a vital role in drafting the recommendations. The subgroup considered and factored in the experiences of people with ME/CFS in making recommendations by considering the high prevalence of co-morbid sleep disorders, the variety of sleep issues, changes with time, abnormal sleep-wake cycles, and the use of sleep aides (e.g. supplements, medications, and treatments) in the selection of our instruments and the design of the case report form.

We prioritized instruments which were shorter in length. The longest instrument (Holland) has 34 items but according to the developers, takes only a median of 7.9 minutes to complete. There were some instruments we evaluated that had many more items but we felt these were not feasible for most ME/CFS patients given that PEM can be triggered by cognitive exertion.

All the instruments chosen were self-administered, written instruments. For certain subgroups, such as cognitively impaired patients or children, such formats may not be optimal. We did evaluate one instrument that was intended to be completed by parents but that instrument was intended for very young children and contained items which were less relevant to ME/CFS. Overall, the subgroup was able to make recommendations that capture the diversity and complexity of the clinical presentations of ME/CFS.