Instructions: This CRF should be completed for any ME/CFS studies where sleep is the primary study outcome.

1. \*Did the subject have a history of sleep problems prior to developing ME/CFS?

☐ Yes

☐ No

* 1. If yes, what was the diagnosis?
  2. If no diagnosis, what issues were present (i.e., sleep disturbance, early wakening, staying asleep, other specify)?

1. \*Was there an acclimation period (e.g. a night when subjects were set up for polysomnography (PSG) but no official measurements taken) or instructions given to subjects before the study began for individual subjects?

☐ Yes

☐ No

1. If yes, describe the acclimation process and/or pre-study instructions. (free text)
2. \*Did the subject take any prescription/ over-the-counter medication, supplements, or herbal preparations regularly to help with their sleep problems?

☐ Yes, complete the medication log.

☐ No

1. \*Did the subject take any neurologic, psychiatric medications, or other medication commonly known to affect sleep?

☐ Yes

☐ No

1. If yes, what medications did the subject take? (List medicines vs. specify drug categories)
2. \*Wereall medications that could affect sleep stopped before the sleep study?

☐ Yes

☐ No

☐ Other instructions given, please specify:

☐ No specific instructions given to subject

1. If ‘yes’ or ‘other instructions given’, how long prior to the study were medications stopped?
2. \*Did sleep / wake times correspond to the subjects' usual sleep/ wake times?

☐ Yes

☐ No

*Note: In prior sleep studies, subjects slept or woke up based on researcher-determined times, which might be very different from what the subject’s usual sleep/wake schedules.*

1. Were objective measures related to heart rate variability employed?

☐ Yes

1. What was measured:
2. Method of measurement:
3. When measures were performed:
4. Describe equipment used:

☐ No

## General Instructions

This CRF contains data that would be collected when sleep is the primary ME/CFS study outcome. Questions #1-6 are classified as Supplemental-Highly Recommended, indicated by an asterisk. Question #7 is classified as Supplemental.

\*Elements are classified as Supplemental-Highly Recommended.

## Specific Instructions

Please see the Data Dictionary for definitions for each of the data elements included in this CRF Module.

The CRF includes all instructions available for the data elements at this time.

* Did the subject have a history of sleep problems prior to developing MECFS? – no additional instructions. Researchers will have to account for and / or separate out the effects of sleep disorders from the effects of ME/CFS on sleep study results
* Was there an acclimation period (e.g. a night when subjects were set up for PSG but no official measurements taken) or instructions given to subjects before the study began for individual subjects? – no additional instructions. (This is a repeat of the following item. Should it be truly deleted?)
* Was there an acclimation period (e.g. a night when subjects were set up for PSG but no official measurements taken) or instructions given to subjects before the study began for individual subjects? - Acclimation in this CRF is defined as a night when subjects were set up for PSG but no official measurements taken. Without an acclimation periods, results from PSG could be a reflection of study participants' adaptation to PSG rather than effects of the ME/CFS itself. Instructions given before a sleep study may also impact results. For example, some researchers have asked study participants to avoid caffeine for 24 hours pre-study.

Use of prescription/ over-the-counter medications, herbal concoctions, and various supplements can affect sleep study results. Consequently it is important for researchers to communicate how these were accounted for in their studies.

* Did the subject take any prescription/ over-the-counter medication, supplements, or herbal preparations regularly to help with their sleep problems? – no additional instructions.
* Did the subject take any neurologic, psychiatric medications, or other medication commonly known to affect sleep? – List medicines vs. specify drug categories in the medication log.
* Were sleep medications stopped before the sleep study? – no additional instructions.
* Did sleep/ wake times correspond to the subjects' usual sleep/ wake times? – no additional instructions. If sleep and wake times in a study are very different from a study participant's usual schedule, these factors can impact results
* Were objective measures related to heart rate variability employed? - In a number of studies, ME/CFS study participants demonstrate lower heart rate variability (HRV) nocturnally compared to controls. Low heart rate variability may be linked to fatigue and unrefreshing sleep. More research to confirm and extend prior work is needed. HRV measures used in prior studies include HRV (heart rate variability), LF power (low-frequency power(ms²)), HF power (high-frequency power(ms²)), LF/HF ratio, TP (Total power(ms²)), RMSSD (root of the mean squares of differences between adjacent R–R intervals), SDNN (standard deviation on R–R intervals), COVR (coefficient of variation), PNN50 (number of pairs of adjacent R–R intervals differing by 450 ms divided by the total number of R–R intervals). Researchers should try to include one if not more of these measures when investigating HRV. HRV can be confounded by many factors and these should be taken into account when designing studies. Some factors that have been identified are age, gender, medication use, presence of a psychiatric condition, physical activity, breathing rate/ frequency, heart disease, and acute stress situations. The equipment used should have been validated against a gold standard like ECG.

References

1. 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.
2. Meeus M, Goubert D, De Backer F, Struyf F, Hermans L, Coppieters I, De Wandele I, Da Silva H, Calders P. Heart rate variability in patients with fibromyalgia and patients with chronic fatigue syndrome: a systematic review. Semin Arthritis Rheum. 2013 Oct;43(2):279-87. doi: 10.1016/j.semarthrit.2013.03.004. Epub 2013 Jul 6.
3. Tak LM, Riese H, de Bock GH, Manoharan A, Kok IC, Rosmalen JG. As good as it gets? A meta-analysis and systematic review of methodological quality of heart rate variability studies in functional somatic disorders. Biol Psychol. 2009 Oct;82(2):101-10. doi: 10.1016/j.biopsycho.2009.05.002. Epub 2009 May 20.
   1. This is an older article. It is being referenced because it contains a table designating elements that should be reported in studies of heart rate variability.