

Guidance for PEM-focused Studies

These data elements apply only to studies whose main purpose is to study post-exertional malaise. As post-exertional malaise consists of multiple symptoms and leads to a reduction in function, specific questionnaires or biomarkers corresponding to these traits should be considered as outcome measures: please see recommendations made by other subgroups for examples of patient-reported outcomes measures, biomarkers, physical examination items, etc. Please also refer to the PEM-focused Studies CRF corresponding to this Guidance.

This guidance assumes that all study participants experience PEM. However, some case definitions do not mandate PEM (e.g. Fukuda 1994 criteria). Studies focused on PEM should recruit subjects who report experiencing PEM as defined in the ME/CFS PEM CDE.

- 1. Documentation of Baseline ME/CFS Symptoms:** Since PEM is defined as an exacerbation of each individual's baseline symptoms, it will be important to know what baseline symptoms each individual experiences. The specific symptoms being evaluated in a given study should be assessed at baseline (pre-exertion) using the same instruments that will be used to evaluate symptoms after exertion. It may be possible to use the assessment of the study participant's symptoms made during the enrollment process or case definition assessment if the same instruments were used, only a short time has elapsed since enrollment, and the instruments are deemed appropriate for documenting symptoms.
- 2. Description of Exertional Stimulus:** The stimulus should be described in enough detail such that other researchers are able to replicate the methods or at least compare other research to it. For researcher-applied stimuli (e.g. treadmill, bike, tilt-table, mentally fatiguing tasks), the type, intensity, frequency, and duration of the stimuli should be detailed. For naturalistic stimuli (i.e. where study participants determine their own level of activity), objective methods such as wearable activity monitoring devices should be used to gauge activity type, intensity, frequency, and duration. Activity monitoring devices should be selected that can accurately assess activity in patients who may be largely recumbent. Less preferably, activity questionnaires could be used.
- 3. Description of Criteria for Termination of Exertional Stimulus:** Criteria will depend on the type of stimulus and the purpose of study but should be detailed enough for replication studies. For example, exertional stimuli may be terminated because of study participant symptoms (e.g. fatigue, pain), pre-determined physiological thresholds (e.g. reaching a specific % of maximum heart rate, respiratory equivalent ratio = 1.0), planned duration (e.g. after 3 days of study participant-determined activity), or natural end to the stimuli (e.g. end of a standardized mentally fatiguing task).

Caution is recommended when considering the use of heart rate (HR) as an index of submaximal effort (ie., % maximal HR) due to the prevalence of orthostatic intolerance, postural orthostatic tachycardia syndrome (POTS), and/or chronotropic incompetence among ME/CFS patients. Using %

maximal HR' as an index of effort or as a standard to compare work intensity in a study of ME/CFS patients could invalidate procedures due to wide individual variability in HR response.

Respiratory exchange ratio (RER), the ratio of carbon dioxide production and oxygen consumption, is an objective indicator of physiological effort that is measured throughout a CPET by collecting and analyzing expired gases (O₂, CO₂). Submaximal effort tests in which heart rate and/or subjective ratings of perceived exertion (RPE) are used to predict endpoints for percentage of maximal effort, should be considered only with a full understanding of the potentially large individual variability in heart rate response in the ME/CFS patient which may be contributed to by both medications and disease pathology.

- 4. Number and Selection of Symptoms Evaluated:** Outcome measures may be study participant self-reported questionnaires, clinician/ researcher assessments, biomarkers, or a combination of these. To qualify as a PEM-focused study, researcher should examine at least physical fatigue, unrefreshing sleep, muscle pain, and problems of concentration and memory. Other common PEM symptoms include cognitive fatigue, tender cervical/ axillary lymph nodes, flu-like malaise, headaches, multi-joint pain, nausea, lightheadedness, general weakness, other sleep disturbances (e.g. problems falling asleep, staying asleep), and more specific cognitive problems (e.g. working memory, multi-tasking). Researchers are also encouraged to study additional symptoms like gut-related symptoms, worsened mood, hypersensitivity to light/sound, etc. that patients have expressed as being part of their PEM but which have not been or rarely studied.
- 5. Patient-reported and Clinician/ researcher-assessed Outcome Measure Characteristics:** These measures should assess not only for presence or absence of symptoms-but also severity, frequency, and duration (as applicable). Here, "clinician/ researcher assessment" refers to questionnaires or instruments that rely on the clinician or researchers' opinion/ judgment, e.g. Clinician Global Improvement Scale, rather than objective tests.
- 6. Assessment of Change of Function/Level of Activity:** In addition to symptom exacerbation, exertion often results in a change of function and/or level of activity, which should be evaluated in parallel with exacerbation of symptoms. Tools which have been used to document these characteristics include the 2-day CPET which determines functional capacity, neuropsychological batteries that evaluate cognitive function, and monitors (e.g. pedometers, actigraphy) that can track the level of activity. While not ideal, activity logs can also be used. Other possible measures include neuroimaging and participant self-report instruments like the Lawton Independent Activities of Daily Living Scale. There is limited and/or equivocal evidence for other measures of function. As with the assessment of exacerbation of symptoms, level of function and activity should be evaluated pre-exertion and again post-exertion.
- 7. Timing of Outcome Measures:** Prior studies show that post-exertional symptoms can start during, immediately after, or hours-days after exposure to a trigger. Studies with 2-day CPET demonstrate a delayed loss of function. Duration can vary from hours, days, weeks, to months. Change in activity or function follows a similar time course. Timing of outcome measures need to reflect what is known

about PEM timing. Most prior studies have tracked symptoms for only 3 to 7 days; such short durations may miss the peak and/or end of PEM symptoms. Consequently, while exact timing and duration of study can be determined by researchers, outcomes should be measured at least four different time points: at baseline (time point 0, before the stimulus is applied), immediately after, at 24 hours after, and at 7 days after the applied stimulus or after the study has started for ecological studies. We also encourage researchers to include time points beyond 7 days to capture episodes of longer-lasting PEM.

- 8. Correlation of Objective Outcome Measures with Subjective Measures:** There is an urgent need for studies where objective outcome measures are studied in conjunction with post-exertional symptoms and change in function/level of activity. Without this type of study design, it is hard to interpret results within the context of symptoms: was the objective outcome measure noted to be at a high, low, absent, or normal level because the participant in fact did not have that symptom as part of their PEM? Or was it being measured at a time when the study participants' PEM had not begun, had not yet peaked, or had already ended? For outcomes measures that are known to be associated with a symptom or symptoms (e.g. decreased pedometer steps with fatigue, increased reaction time with slowed information processing speed), these outcomes should be measured at or around the same time as patient-reported outcome measures corresponding to them (e.g. for the former examples, self-report instruments assessing fatigue or cognitive issues). Researchers are also encouraged to investigate links between any objective measure and subjective symptoms as there may be as-yet undiscovered objective measures which track with PEM symptoms.
- 9. Confounding Activity and PEM:** Confounding activity means activity spontaneously engaged in by study participants which is not intended to induce PEM. Researchers should document what instructions were given to study participants regarding activity before the PEM study commenced or, conversely, establish the pre-study activity level of study participants via monitors or questionnaires. Similarly, participant instructions and/or documentation of activity while the study is occurring is also required. Study participant activity in the periods before and during the time of study can induce additional PEM, beyond that planned for or measured (in the case of naturalistic study design with only intermittent activity monitoring) by researchers, and affect results. Researchers should also be aware that many people affected by ME/CFS often modify, reduce, or restrict their activities - a practice called pacing - to control PEM initiation or severity. The potential impact of pacing needs to be considered and managed depending on a study's purpose and design.
- 10. Risks associated with PEM studies:** PEM studies may result in participants requiring prolonged periods (hours, days, weeks or even longer) to return to their pre-study baseline of health and function. It is also possible that some patients may not return to their baseline status. The benefits and risks of these studies need to be clearly communicated to potential study participants, as it can be difficult to predict for any individual person how severe or prolonged their PEM may be. As we learn more about the pathophysiology of PEM, researchers should also attempt to mitigate the effects of severe or prolonged PEM resulting from studies.