

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

Subgroup Statement of Purview

The NINDS/CDC ME/CFS Common Data Elements Post-Exertional Malaise (PEM) Subgroup will consider PEM from two perspectives: patient-reported symptoms and concomitant objective outcomes. The definition of PEM used in the common data element recommendations is based on the National Academy of Medicine (NAM, previously called the Institute of Medicine), Systemic Exertion Intolerance Disease (SEID) criteria the Canadian Consensus Criteria, and the ME International Consensus Criteria, where PEM is called post-exertional neuroimmune exhaustion (PENE).

PEM is defined as an abnormal response to minimal amounts of physical or cognitive exertion that is characterized by:

1. Exacerbation of some or all of an individual study participant's ME/CFS symptoms. Symptoms exacerbated can include physical fatigue, cognitive fatigue, problems thinking (e.g. slowed information processing speed, memory, concentration), unrefreshing sleep, muscle pain, joint pain, headaches, weakness/instability, light-headedness, flu-like symptoms, sore throat, nausea, and other symptoms. Study participants can experience new or non-typical symptoms as well as exacerbation of their more typical symptoms.
2. Loss of stamina and/or functional capacity
3. An onset that can be immediate or delayed after the exertional stimulus by hours, days or even longer.
4. A prolonged, unpredictable recovery period that may last days, weeks, or even months.
5. Severity and duration of symptoms that is often out-of-proportion to the type, intensity, frequency, and/or duration of the exertion. For some study participants, even basic activities of daily living like toileting, bathing, dressing, communicating, and reading can trigger PEM.

Some other precipitants of PEM that have been identified include positional changes and emotional stress. In some instances, the specific precipitant cannot be identified. The threshold for a precipitant to trigger PEM can vary between individuals as well as within the same individual, at different times during their illness.

These recommendations will comprise patient-reported questionnaires, research and clinic-based report forms, and objective tests researchers can use to a) identify the existence of PEM for use in case assessment, b) consistently and systematically capture the various ways PEM is experienced by study participants and c) capture the effect of exertion on various symptoms and d) assess the relationship of PEM and objective measures of physiological changes, for example those in gene expression, brain function, and energy metabolism.

Reference: IOM report, pages #78-80

The approach taken for developing the post-exertional malaise (PEM) materials was based on the importance of PEM in ME/CFS. The committee members used their clinical/ research experience, knowledge of existing tools, and a review of the relevant literature in order to understand the range of symptoms experienced as part of PEM, the strengths and weaknesses of existing tools for assessment of PEM in ME/CFS, and the strengths and weaknesses of current research approaches into PEM. Several working group members have personal experience with ME/CFS, as patients or as carers. The subgroup heard directly from members who have a personal experience with the disease and reviewed studies/ reports which directly queried people with ME/CFS about their experiences. Additionally, the majority of subgroup members had experienced directly working with people with ME/CFS. This led the PEM Subgroup to focus on the following requirements:

1. Agree upon a definition for PEM:

Please see the Purview and the “Short Description of the Instrument” section of the NOC for the definition.

2. Provide a standard method for assessing PEM across all ME/CFS studies

The National Academy of Medicine (previously called the Institute of Medicine) Systemic Exertion Intolerance Disease (SEID) criteria, the Canadian Consensus Criteria, and the ME International Consensus Criteria define PEM as a required criterion of ME/CFS. To ensure comparability of research studies, all research studies need to use a consistent tool to ascertain the presence of PEM in research participants.

The 2-day cardiopulmonary exercise test (CPET) objectively demonstrates the loss of function that occurs following exertion but does not evaluate the exacerbation of symptoms that is also part of PEM. Further, the test cannot be used across all studies because of cost, expertise, the level of severity of some participants, and other factors. There are also few well-tested patient-reported tools specifically designed to ascertain PEM. The DePaul Symptom Questionnaire (DSQ), has been tested and used in several ME/CFS studies, has been evaluated in multiple diseases, includes a PEM subscale, and has been used by different researchers. The PEM subscale of the DSQ was chosen as the basis of the Core CDE Instrument and associated Case Report Form for assessing PEM in all study participants across all ME/CFS studies.

3. Provide recommendations for PEM-focused studies

Existing studies of PEM often miss or do not report important aspects of PEM. To expedite progress on research into PEM, recommendations for PEM-focused studies have been developed to more consistently and systematically capture the effect of exertion on various symptoms, on loss of functional ability, on delayed recovery, and on various physiological measures.

The recommendations for PEM-focused studies include guidance on the number/ choice of symptoms to be assessed, the description of exertional stimuli, methods for assessing change in symptoms and function, and the timing of measures. The guidance also discusses the need to correlate subjective and objective measures and to consider activities that could confound the evaluation of PEM. We also developed a CRF corresponding to the guidance document to further assist researchers in completing the items mentioned.

The use of the 2-day CPET will be covered by the Quality of Life group. Please refer to that subgroup's documents for more information about 2-day CPET.

The benefits and risks of studies intended to trigger PEM 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. Additionally, many ME/CFS patients use strategies to avoid and/or to minimize the impact of PEM. We did not discuss the methods to be used in research into the management and/or treatment of PEM.

The subgroup was not able to make recommendations that capture the diversity and complexity of the clinical presentations of ME/CFS. The recommendations are more appropriate for patients who are not severely ill. Studies of PEM in severely ill patients will need to consider the level of functioning in these patients and the risk of exacerbating their condition.

While there is little formal research on subtypes of ME/CFS as it pertains to PEM, severely impaired patients may experience PEM with significantly smaller levels of exertion. Recommendations made by this working group may need to be modified or adapted for this group. Studies of PEM in this subgroup may require different approaches for the level and type of exertional stimulus, the types of subjective and objective outcomes measures, and additional consideration of the ways in which confounding factors might affect the assessment of PEM. It should also be noted that almost all PEM studies have been based on adults and the DSQ has not been tested in children.

Our recommendations for PEM-focused studies assume that all study participants experience PEM. However, if the 1994 Fukuda et al definition is being used, some study participants may not experience PEM as Fukuda does not require it. Studies focused on PEM should recruit subjects who report experiencing PEM.

The materials recommended by this subgroup include:

- Guidance for Core PEM Assessment to assess the presence of PEM as a case defining criteria in all study participants
- Core PEM Assessment Questionnaire to use in conjunction with the Guidance for Core PEM Assessment Instrument
- Guidance for PEM-focused Studies that discusses considerations in the design, conduct, and analysis of studies focused on PEM
- PEM-focused Studies Questionnaire corresponding to the Guidance for PEM-focused Studies

Consideration was given to the burden and/or acceptability of instruments to people with ME/CFS. The DSQ PEM subscale is a brief 5-item self-administered, written questionnaire that has been used previously with success in ME/CFS participants. We recognize the instrument's format may not be feasible/ acceptable to some subgroups of patients (e.g. children, severely affected patients who are unable to read/ write). These subgroups may require, for example, a carer to respond instead or an aural/ oral format. We encourage researchers to investigate these issues in the future. Other parts of the Core PEM Assessment and the PEM-focused Studies CRF are to be completed by researchers.

The 2015 National Academy of Medicine report stated, "PEM is an exacerbation of some or all of an individual's ME/CFS symptoms that occurs after physical or cognitive exertion and leads to a reduction in functional ability." The NAM report defined PEM to be a hallmark of ME/CFS, mandated it for the SEID case definition, and discussed its range of symptoms, variety of triggers, and chronological course. The Canadian Consensus Criteria and the ME International Consensus Criteria, both of which have been used in research, define PEM in similar ways. The Core PEM CDE and the guidance for PEM-focused studies have been based on the descriptions of PEM provided in these standards.

The 2012 [Minimal Data Elements for Research Reports on CFS](#), by Jason et al. described PEM as a ‘key’ symptom and specifically suggested the use of activity measurement as additional measures for PEM in order to assess the extent of activity and how such activity might result in exacerbation of symptoms. These measures include

- Maximal or Submaximal Exercise Challenge
- Actigraphy
- Time Logs (ACTRE)

These recommendations have been incorporated into the guidance for PEM-focused studies.

Issues unique to ME/CFS or which highlight a unique concern about ME/CFS data collection encountered when developing the CDE standards were:

- a. The definition of PEM is based primarily on clinician experience, patient reports and a few formal studies. There is a dearth of studies asking participants about their experiences of PEM in an open-ended manner, which is needed. There is also a lack of research on PEM in subgroups like the severely ill patients, ethnic minorities, the elderly and children.
- b. Much more study is needed on PEM in general. Weaknesses or limitations of past studies include lack of exploration of PEM triggers beyond physical activity, focus on only 1-2 symptoms when PEM encompasses multiple symptoms, focus on primarily pain and fatigue-related symptoms, utility of patient-reported outcome measures as the sole outcomes, brief follow-up times, and the need for more studies that test the associations between patient-reported symptoms with other outcomes and with physiological responses. See the Guidance for PEM-focused Studies for a more detailed discussion.
- c. Both a. and b. contribute to the lack of patient-reported and other well-validated outcome measures specifically designed to measure PEM. Many show promise but lack of evaluation of these measures specifically to assess the symptom of PEM-precludes us from recommending specific instruments or outcomes, other than the DSQ, as “core” or “highly recommended.”
- d. This should not discourage researchers from attempting to adapt and test already-existing patient-reported or other outcome measures for use in ME/CFS, testing the Exploratory outcome measures mentioned, or devising new outcome measures. In fact, we would encourage all these steps.

Studies should include objective outcome measures that go beyond patient-reported or researcher-assessed measures (e.g. Clinician Global Impression Scale). Currently, there exists no patient-reported outcome measure that is both specifically designed for and covers comprehensively the characteristics of PEM. Such an instrument is urgently needed. Other unmet needs include:

1. The currently recommended Core PEM Assessment Instrument to assess the presence or absence of PEM across all studies uses the PEM subscale of the DSQ. This was chosen because it is the only suitable existing instrument. However, it is recognized that DSQ has some limitations, particularly in terms of the breadth of the symptoms covered, and in its ability to detect PEM triggered by stressors other than physical activity. Patients who already modify their activities to avoid or reduce PEM may potentially show up as false-negatives on the PEM subscale. Therefore, the further development, refinement and validation of a tool is a priority that needs to be addressed as quickly as possible.
2. Further development, refinement and validation of this Core PEM Instrument and CRF and of other PEM patient-reported outcome measures is needed including a) inclusion of additional symptoms and chronological features, b) comparison to other diseases that have a similar

symptom/ clinical presentation, c) validation of instruments specifically for the symptom of PEM, d) creation of instruments appropriate for children, and e) incorporation of physical, mental, and other types of stressors to investigate whether different precipitants may lead to divergent PEM patterns.

3. Studies to better characterize the key features of PEM including the breadth of symptoms experienced, measures of change in function/activity, delayed onset and recovery, and the relationship between PEM and various physiological measures such as gene expression, plasma cytokines, and cardiorespiratory fitness.
4. Studies of PEM in severely ill patients, children, the elderly, ethnic minorities, and other underrepresented groups.
5. Studies to identify and validate a biomarker(s) that correlates with PEM
6. Studies of treatments to prevent, stop, or mitigate PEM. This includes both behavioral measures, such as balancing activity with rest (commonly termed “pacing”), as well as pharmacologic treatments.