

Public Review

**Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
(ME/CFS)**

Common Data Elements (CDE)

Post-Exertional Malaise Subgroup Materials

Table of Contents

POST-EXERTIONAL MALAISE SUBGROUP SUMMARY.....	2
PEM STATEMENT OF PURVIEW	7
CORE PEM ASSESSMENT CASE REPORT FORM (CRF).....	8
DEPAUL SYMPTOM QUESTIONNAIRE (DSQ) PEM SUBSCALE.....	8
PEM-FOCUSED STUDIES CRF	12
GUIDANCE FOR PEM-FOCUSED STUDIES.....	19
PEM-FOCUSED EXPLORATORY OUTCOME MEASURES	27
PEM SUBGROUP ROSTER	28

NINDS CDE Project

Subgroup in ME/CFS: Post Exertional Malaise

Completed by:

Date:

Please answer the following questions below.

- 1. Approach for selection of elements** (*How did you go about drafting the recommendations and/or reviewing the current tools/instruments, and did you have any criteria for selection and classification?*)

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.

The led the PEM CDE team 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.

2. Differential application to types of ME/CFS (*Do the instruments/elements you recommended differ between the types of ME/CFS?*)

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.

3. Summary recommendations (*We could consider a summary table OR each group could summarize their recommendations*).

The materials recommended by this subgroup include:

- Core PEM Assessment Instrument to assess the presence of PEM as a case defining criteria in all study participants
- Core PEM Assessment Case Report Form to use in conjunction with the 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 CRF corresponding to the Guidance for PEM-focused Studies
- PEM Exploratory Measures Case Report Form concerning the use of activity monitors in PEM-focused studies

4. Comparison to other ME/CFS standards *(Are there any notable similarities/differences in the CDE recommendations as compared with other standards?)*

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.

5. Issues unique to ME/CFS *(Were there any issues encountered when developing the CDE standards which are unique to ME/CFS or which highlight a unique concern about ME/CFS data collection?)*

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.

6. Unmet needs; unanswered questions (*What unmet need / unanswered questions were identified via the CDE process in ME/CFS? What areas are in need of further research and development?*)

Studies should include objective outcome measures that go beyond patient-reported or researcher-assessed measures (e.g. Clinician Global Impression Scale). Other unmet needs include:

1. Further development and refinement of the Core PEM Instrument and CRF and other PEM patient-reported outcome measures including a) inclusion of additional symptoms and chronological features, b) studies in other diseases that have a similar symptom presentation, c) validation of instruments specifically for the symptom of PEM and d) instruments appropriate for children
2. 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.
3. Studies of PEM in severely ill patients, children, the elderly, ethnic minorities, and other underrepresented groups.
4. Studies to identify and validate a biomarker(s) that correlates with PEM
5. 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.

7. **Patient Advocates Only**

- a. What role did people with ME/CFS play in the drafting of recommendations?
Several working group members have personal experience with ME/CFS, as patients or as carers.
- b. How did the subgroup consider and factor in the experiences of people with ME/CFS in making recommendations?
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.
- c. What 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 Instrument and the PEM-focused Studies CRF are to be completed by researchers.

- d. Was the subgroup able to make recommendations that capture the diversity and complexity of the clinical presentations of ME/CFS?

No. 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.

- e. Can you identify specific needs or gaps? (e.g., specific need for an instrument to assess pain that is easier for patients to complete)?

As mentioned above, patients' experiences of PEM, and the relation of that experience to physiological changes, need to be directly explored in more studies, including studies of severely ill patients and children with ME/CFS. 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.

NINDS/CDC ME/CFS Common Data Elements Post-Exertional Malaise Subgroup

Draft 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 or days but the exact timing is not well understood.
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

Core PEM Assessment CRF

[Study Name/ID pre-filled]

Site Name:

Subject ID:

This CRF is used to support the Core DePaul Symptom Questionnaire (DSQ) PEM Subscale Instrument and is used in all studies.

*For the following questions, we would like to know **how often you have had each symptom** and **how much each symptom has bothered you over the last 6 months**.*

For each symptom please circle one number for frequency and one number for severity. Please fill the chart out from left to right.

Symptom	<u>Frequency</u>	<u>Severity</u>
	<p>Throughout the past 6 months, how often have you had this symptom?</p> <p>For each symptom listed below, circle a number from:</p> <p>0 = none of the time</p> <p>1 = a little of the time</p> <p>2 = about half the time</p> <p>3 = most of the time</p> <p>4 = all of the time</p>	<p>Throughout the past 6 months, how much has this symptom bothered you?</p> <p>For each symptom listed below, circle a number from:</p> <p>0 = symptom not present</p> <p>1 = mild</p> <p>2 = moderate</p> <p>3 = severe</p> <p>4 = very severe</p>
1. Dead, heavy feeling after starting to exercise	0 1 2 3 4	0 1 2 3 4
2. Next day soreness or fatigue after non-strenuous, everyday activities	0 1 2 3 4	0 1 2 3 4
3. Mentally tired after the slightest effort	0 1 2 3 4	0 1 2 3 4
4. Minimum exercise makes you physically tired	0 1 2 3 4	0 1 2 3 4

Core PEM Assessment CRF

[Study Name/ID pre-filled]

Site Name:

Subject ID:

5. Physically drained or sick after mild activity	0 1 2 3 4	0 1 2 3 4
---	-----------	-----------

6. Was the DSQ PEM Threshold met?

- No
- Yes

7. What method was used to determine whether the study participant experiences PEM?
(Please check all answers that apply.)

- The 2-step DSQ PEM/researcher evaluation process (recommended)
- Previously reported by a ME/CFS specialist
- Previously reported by other medical provider who is not an ME/CFS specialist
- Patient-reported - using DSQ PEM questions
- Patient-reported - other sources
- Other, specify _____

8. Does the study participant experience PEM?

- No
 - Yes
 - Inconclusive
 - Not Evaluated
-

Core PEM Assessment CRF Module Instructions

GENERAL INSTRUCTIONS

This CRF Module is used to support the Core DePaul Symptom Questionnaire (DSQ) PEM Subscale Instrument and is recommended as Core for all ME/CFS studies.

SPECIFIC INSTRUCTIONS

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

- Timeframe to assess symptoms: The severity and frequency of symptoms should be assessed over the last 6 months.
- Scoring algorithm: A frequency of at least 2 and a severity of at least 2 on any one of the 5 questions on the DSQ PEM subscale indicates that PEM is present. If the study participant meets this threshold, the DSQ PEM Threshold is set to “Yes;” otherwise it is set to “No.” A frequency of 2 on one question and a severity of 2 on a separate question does not satisfy this threshold.
- Guidance on “PEM Determination Method:” The standard method for evaluating the “Global PEM Determination” is a two step process in which the study participant responds to the DSQ PEM questions and the researcher then evaluates those responses in light of other information about the study participant to determine whether the study participant has PEM or not. In making this determination, the researcher or clinician will need to consider whether there are other conditions, such as overwork, that could result in a false positive DSQ PEM subscale response. On the other hand, the researcher or clinician should also consider whether the study participant responded negatively because, for instance, they carefully manage their energy expenditures with pacing to avoid episodes of PEM. In addition to asking questions about workload and pacing, the researcher may also ask what happens to the study participant if/when they engage in physical or mental activity and whether there are activities they avoid because it exacerbates symptoms. In addition to their own examination of the study participant, the researcher may also consider information from sources like medical records but these should be carefully considered, as they might not reflect an accurate understanding of the nature of PEM.

While the above method should be used in all studies, there may certain types of studies, such as patient surveys or studies of existing samples in which it is not possible to use this two-step method. In those limited instances, the researcher may be able to use information from other sources, such as patient reports and medical records as the basis of the Global PEM Determination. These other choices, particularly self-report and reports by other medical providers, are not recommended because these reports of PEM have not been verified.

- The following choices are provided to capture the method used to determine PEM:
 - o The 2-step DSQ PEM/researcher evaluation process (recommended)
 - o Previously reported by ME/CFS Specialist
 - o Previously reported by other Medical Provider who is not an ME/CFS specialist
 - o Patient reported - using DSQ PEM questions
 - o Patient-reported – other sources

Core PEM Assessment CRF Module Instructions

- o Other, specify

Multiple choices can be selected if appropriate. The first choice should only be selected when the two-step process described above is used.

- Guidance on “Global PEM Determination:” Regardless of the method used as described in the previous section, the presence or absence of PEM is captured in this field using one of the following choices:
 - Yes
 - No
 - Inconclusive
 - Not Evaluated

REFERENCES

Klimas NG, Ironson G, Carter A, Balbin E, Bateman L, Felsenstein D, Levine S, Peterson D, Chiu K, Allen A, Cunningham K, Gottschalk CG, Fletcher M, Hornig M, Canning C & Komaroff AL. Findings from a clinical and laboratory database developed for discovery of pathogenic mechanisms in myalgic encephalomyelitis/chronic fatigue syndrome, *Fatigue: Biomedicine, Health & Behavior*. 2015;3(2):75-96.

Jason LA, So S, Brown AA, Sunnquist M, Evans M. Test-Retest Reliability of the DePaul Symptom Questionnaire. *Fatigue : biomedicine, health & behavior*. 2015;3(1):16-32.

Jason LA, Sunnquist M, Brown A, et al. Examining case definition criteria for chronic fatigue syndrome and myalgic encephalomyelitis. *Fatigue : biomedicine, health & behavior*. 2014;2(1):40-56.

Brown A, Jason LA. Validating a measure of myalgic encephalomyelitis/chronic fatigue syndrome symptomatology. *Fatigue*. July 2014; 2(3): 132–152.

Strand EB, Lillestøl K, Jason LA, Tveito K, Diep LM, Valla SS. Comparing the DePaul Symptom Questionnaire with physician assessments: a preliminary study. *Fatigue: Biomedicine. Health Behav*. 2016;4(1):52–62.

Murdock KW, Wang XS, Shi Q, Cleeland C, Fagundes C, Vernon S. The utility of patient-reported outcome measures among patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Qual Life Res*. 2017;26(4):913-921.

Jason LA, Sunnquist M, Brown A, Furst J, Cid M, Farietta J, Kot B, Bloomer C, Nicholson L, Williams Y, Jantke R, Newton J, Strand E. Factor analysis of the DePaul Symptom Questionnaire: Identifying core domains. *Journal of Neurology and Neurobiology*. 2015;1(4):1–9.

Institute of Medicine. (2015). *Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness*. Washington (DC): National Academies Press (US), p. 82.

NINDS CDE Notice of Copyright

DePaul Symptom Questionnaire (DSQ) Post-Exertional Malaise Subscale

<p>Availability:</p>	<p>Please visit this website for more information about the instrument: Post-Exertional Malaise (PEM) subscale questions from the DePaul Symptom Questionnaire (DSQ) can be downloaded from the REDCap shared library. It can be viewed here: https://redcap.is.depaul.edu/surveys/?s=tRxytSPVVw. The author, Dr. Leonard Jason, has granted permission for its use and the DSQ is already in use in the field.</p>
<p>Classification:</p>	<p>Core: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)</p>
<p>Short Description of Instrument:</p>	<p>The “PEM Determination” is a Core CDE instrument to be used across <i>all</i> research studies as a common method for ascertaining and recording the presence or absence of PEM as a case defining symptom in each individual study participant.</p> <p>Construct measured: Post-Exertional Malaise (PEM).</p> <p>Generic vs. disease specific: Disease Specific.</p> <p>Means of administration: Written. Patient self-report plus Researcher/Clinician Evaluation.</p> <p>Intended respondent: Study Participant and Researcher/Clinician.</p> <p># of items: 14</p> <p># of subscales and names of sub-scales: 2 – Post-Exertional Malaise scale of the DSQ and indicator questions</p> <p># of items per sub-scale: 10 for the DSQ and 4 for the indicator questions</p> <p>Administration: The study participant indicates the severity and frequency of 5 statements about post-exertional malaise over the last six months. The researcher/clinician then reviews the responses along with any other information they may have (e.g. medical records, medical interview responses, physical examination findings, etc.) and records whether they deem the study participant to have experienced PEM.</p>
<p>Background:</p>	<p>In its 2015 report, the National Academy of Medicine (NAM, previously called the Institute of Medicine) established PEM as a hallmark symptom of ME/CFS and required it for a diagnosis. The Canadian Consensus Criteria and the ME International Consensus Criteria also require this symptom.</p> <p>Post-exertional malaise is an abnormal response to minimal amounts of physical or cognitive exertion that is characterized by:</p> <ul style="list-style-type: none"> i. Exacerbation of some or all of an individual study participant's ME/CFS symptoms. Symptoms exacerbated can include physical fatigue,

NINDS/CDC Notice of Copyright

DePaul Symptom Questionnaire (DSQ) Post-Exertional Malaise Subscale

	<p>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.</p> <ul style="list-style-type: none">ii. Loss of stamina and/or functional capacityiii. An onset that can be immediate or delayed after the exertional stimulus by hours, days, or even weeksiv. A prolonged, unpredictable recovery period that may last days, weeks, or even months.v. 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. <p>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.</p> <p>Assessing PEM: Because of PEM’s importance as a case-defining criteria, it is essential to have a consistent method for ascertaining the presence or absence of PEM in all research study participants, regardless of the research case definition used.</p> <p>The recommended core method for assessing PEM is a 2-step process in which the study participant responds to the DSQ PEM questions and the researcher then evaluates those responses in light of other information (e.g. study participant interview, physical examination, objective testing) about the study participant to determine whether the study participant experiences PEM or not.</p> <p>Under certain circumstances, some studies, such as those using historical data, may not be able to use this two-step method. In those limited instances, the researcher may be able to use information from other sources, such as other non-DSQ patient self-report instruments and medical records, as the basis of the PEM Determination.</p> <p>Whether the 2-step process is used or not, all studies will use the core PEM CDE which includes the following four components:</p> <ul style="list-style-type: none">1. Patient response to five questions of the PEM subscale of the DePaul Symptom Questionnaire.<ul style="list-style-type: none">a. Dead, Heavy feeling after starting to exercise
--	--

DePaul Symptom Questionnaire (DSQ) Post-Exertional Malaise Subscale

- b. Next day soreness or fatigue after non-strenuous, everyday activities
- c. Mentally tired after the slightest effort
- d. Minimum exercise makes you physically tired
- e. Physically drained or sick after mild activity

Each question is scored for frequency and for severity.

Frequency is scored as:

Severity is scored as:

0 = none of the time

0 = symptom not present

1 = a little of the time

1 = mild

2 = about half the time

2 = moderate

3 = most of the time

3 = severe

4 = all of the time

4 = very severe

2. DSQ PEM Threshold – a single data field to capture whether the responses to the DSQ PEM questions met the required threshold of severity=2 and frequency=2 on any one question. To be filled in by the researcher. Choices are Yes/No.
3. PEM Determination Method – a single data field to capture how the researcher determined whether the study participant experiences PEM. The recommended standard method is the two-step process of the DSQ PEM subscale plus the researcher’s evaluation. If that method cannot be used but the researcher has other information that indicates whether PEM exists or not, those methods can also be indicated as follows:
 - a. The 2-step DSQ PEM/researcher evaluation process (recommended)
 - b. Previously reported by ME/CFS specialist
 - c. Previously reported by other medical provider who is not an ME/CFS specialist
 - d. Patient reported - using DSQ PEM questions
 - e. Patient reported – using non-DSQ methods
 - f. Other SpecifyResearchers may choose more than one option as needed to best reflect the methods they used.
4. Global PEM Determination – a single data field to capture the final determination of whether the study participant experiences PEM on not. The researcher or clinician will need to consider whether there are other conditions, such as an excessive workload, that could result in a false positive DSQ PEM subscale response. This field should be completed regardless of what determination method was used. Choices are:

NINDS/CDC Notice of Copyright

DePaul Symptom Questionnaire (DSQ) Post-Exertional Malaise Subscale

	<p>a. Yes b. No c. Inconclusive d. Not Evaluated</p> <p>Please see the “General Instructions for the CRF” for further details.</p> <p>Together, these components will produce 14 data elements, 10 for the five questions one each for <i>DSQ PEM Threshold</i> and <i>Global PEM Determination</i>, and one or two for <i>PEM Determination Method</i> (<i>the second to provide a place to capture other methods if specified</i>).</p>
<p>Scoring:</p>	<p>Scoring Algorithm for DSQ PEM Subscale: A frequency of at least 2 and a severity of at least 2 on any one of the 5 questions on the DSQ PEM subscale indicate that PEM is present. If the study participant response meets this threshold, the DSQ PEM Threshold is set to “Yes;” otherwise it is set to “No.” A frequency of 2 on one question and a severity of 2 on a separate question does not satisfy this threshold.</p> <p>Please also see the “General Instructions for the CRF” for further details.</p>
<p>Rationale/ Justification:</p>	<p>As noted in the 2015 National Academy of Medicine report on ME/CFS, post-exertional malaise (PEM) “is a primary feature that helps distinguish ME/CFS from other conditions.” . While the 1994 Fukuda et al definition does not require PEM, newer definitions do. However, to date, different researchers have operationalized PEM differently. The NAM report noted this problem and stated, “Use of a standardized instrument is critical to measuring PEM accurately because differences in wording on various self-report items have been shown to change the prevalence of PEM in the same group of patients.” For instance, Jason found that the prevalence of PEM ranged from 25% of the study participants to 100% in a review of 53 studies.</p> <p>To avoid this issue going forward, ME/CFS research requires a standard method used across all studies, to determine whether a given study participant experiences PEM or not. To meet this need, the NIH ME/CFS PEM subgroup has recommended a core CDE to identify the existence of PEM for use in case assessment. This core instrument is to be used across all studies.</p> <p>In its report, the NAM only recommended three tools to identify PEM: the 2-day CPET, the DePaul Symptom Questionnaire, and the CDC symptom inventory. The 2-day CPET is an objective measure of the loss of function and delayed recovery. CPET has a significant body of research across multiple groups and is used in disability assessments. But it cannot be used in studies of severely ill study participants and may not be used in all studies because of cost and the expertise</p>

DePaul Symptom Questionnaire (DSQ) Post-Exertional Malaise Subscale

required to perform the test. The CDC Symptom Inventory asks a set of questions about “fatigue after exertion.” However, PEM is more than just fatigue after exertion. The PEM subscale of the DSQ presents a broader view of PEM. The DSQ has been used by various research groups and has a considerable body of research on its psychometric properties. Finally, it has been translated to multiple languages including Spanish.

Beyond these three tools, no other instruments have been used and validated for the specific purpose of identifying the presence of PEM. While not perfect, the PEM subscale of DSQ is the best choice at this time for a standard method of identifying the existence of PEM in a research study participant.

Strengths/ Weaknesses:

Limitations

The limitations of this scale include the following:

- The instrument does not assess the full range of symptoms that could be exacerbated by PEM and only one item addresses the sometimes delayed onset/ prolonged duration of PEM ("Next day soreness or fatigue after non-strenuous, everyday activities.")
- The studies published to date primarily evaluate the DSQ in ME/CFS compared to healthy controls, not in other fatiguing conditions or conditions where there could be diagnostic ambiguity. Recent research has shown a difference between ME/CFS and MS study participants.
- The use of the DSQ PEM subscale as a stand-alone instrument has not been separately validated although as noted above, its use has resulted in a high prevalence of PEM being reported in ME/CFS study participants.
- The instrument will need to be further evaluated to ensure it accurately reflects the symptom of PEM. This should be done in concert with objective measures of the disease as well as objective measures of loss of function and symptom exacerbation when those are available.

Further research is needed to address these limitations.

Strengths including Psychometric Properties:

Construct validity was established via factor analysis. The PEM items loaded onto the same factor in an initial factor analytic study [1], indicative of strong construct validity, and this finding was subsequently replicated with a larger sample [2]. In both studies, the PEM factor evidenced convergent validity in its significant negative correlation with SF-36 Physical Health Subscales ($r \leq -0.68$).

DePaul Symptom Questionnaire (DSQ) Post-Exertional Malaise Subscale

	<p>Reliability: Test-retest: Pearson’s correlation coefficients = 0.85 or higher. Internal consistency: Cronbach’s alpha = 0.88 [1] and 0.95 [2].</p> <p>While the PEM subscale has not been validated as a stand-alone tool, the full DSQ has been used broadly in ME/CFS research and its performance evaluated by both Jason and also by other researchers, including in cohorts selected by disease experts. Examples include</p> <ul style="list-style-type: none"> ● Jason et al has demonstrated good test-retest reliability of the DSQ. ● Jason et al reported that housebound study participants had significantly higher scores on the DSQ PEM items than participants who were not housebound. This suggests that more severely patients will have higher scores. ● Klimas et al evaluated different components of the DSQ (including the PEM/fatigue set of questions) in a cohort of study participants selected by disease experts. ● Murdock found that the full DSQ showed excellent internal consistency, sensitivity, and specificity and did not show the ceiling effects demonstrated in some instruments. ● <p>The DSQ calls for an evaluation of symptoms over the last 6 months and this time frame results in the most reliable data.</p> <p>Other Research using the DSQ PEM Subscale</p> <p>Murdock et al also evaluated the performance of a set of eight questions that included the five on the PEM subscale, plus fatigue, unrefreshing sleep, and muscle weakness and found it had excellent utility excellent clinical utility” in differentiating between ME/CFS and controls. However, it is not appropriate as a stand-alone tool to evaluate the presence of PEM because the responses to the Murdock questions on fatigue, unrefreshing sleep, and muscle weakness could result in a positive response even if the post-exertion questions were all negative.</p>
<p>References:</p>	<p>Key Reference:</p> <p>Jason LA, So S, Brown AA, Sunquist M, Evans M. Test-Retest Reliability of the DePaul Symptom Questionnaire. <i>Fatigue : biomedicine, health & behavior</i>. 2015;3(1):16-32.</p> <p>Additional References:</p> <p>Brown A, Jason LA. Validating a measure of myalgic encephalomyelitis/chronic fatigue syndrome symptomatology. <i>Fatigue</i>. July 2014; 2(3): 132–152.</p>

DePaul Symptom Questionnaire (DSQ) Post-Exertional Malaise Subscale

	<p>Klimas NG, Ironson G, Carter A, Balbin E, Bateman L, Felsenstein D, Levine S, Peterson D, Chiu K, Allen A, Cunningham K, Gottschalk CG, Fletcher M, Hornig M, Canning C & Komaroff AL. Findings from a clinical and laboratory database developed for discovery of pathogenic mechanisms in myalgic encephalomyelitis/chronic fatigue syndrome, <i>Fatigue: Biomedicine, Health & Behavior</i>. 2015;3(2):75-96.</p> <p>Institute of Medicine. (2015). <i>Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness</i>. Washington (DC): National Academies Press (US), p. 82</p> <p>Jason LA, Ohanian D, Brown A, et al. Differentiating Multiple Sclerosis from Myalgic Encephalomyelitis and Chronic Fatigue Syndrome. <i>Insights Biomed</i>. 2017, 2:2.</p> <p>Jason LA, Sunnquist M, Brown A, Furst J, Cid M, Farietta J, Kot B, Bloomer C, Nicholson L, Williams Y, Jantke R, Newton J, Strand E. Factor analysis of the DePaul Symptom Questionnaire: Identifying core domains. <i>Journal of Neurology and Neurobiology</i>. 2015;1(4):1–9.</p> <p>Jason LA, Sunnquist M, Brown A, et al. Examining case definition criteria for chronic fatigue syndrome and myalgic encephalomyelitis. <i>Fatigue : biomedicine, health & behavior</i>. 2014;2(1):40-56.</p> <p>Murdock KW, Wang XS, Shi Q, Cleeland C, Fagundes C, Vernon S. The utility of patient-reported outcome measures among patients with myalgic encephalomyelitis/chronic fatigue syndrome. <i>Qual Life Res</i>. 2017;26(4):913-921.</p> <p>Strand EB, Lillestøl K, Jason LA, Tveito K, Diep LM, Valla SS. Comparing the DePaul Symptom Questionnaire with physician assessments: a preliminary study. <i>Fatigue: Biomedicine. Health Behav</i>. 2016;4(1):52–62.</p>
--	--

PEM-focused Studies CRF

[Study Name/ID pre-filled]

Site Name:

Subject ID:

- 1) ***Describe the exertional stimulus used to induce PEM. Check all answers that apply.**
- a) *Type:
- I. Physical exertion
 - II. Cognitive exertion
 - III. Orthostatic
 - IV. Other
- (Please specify: _____)
- b) *Was stimulus researcher-applied/ determined or study-participant-determined (i.e. spontaneous/ free activity)?
- Researcher
 - Study participant
 - Both
 - Neither
- c) *For researcher-applied/ determined stimulus, please describe the stimulus.
- I. Type (e.g. treadmill, bicycle, cognitive-fatiguing activity):
 - II. Protocol for stimulus (e.g. Bruce protocol for treadmill; intensity, frequency, duration):
- d) *For study-participant-determined stimulus, please describe how stimulus was measured or characterized (e.g. pedometer steps, activity diary, etc.):
- I. Activity Diary
 - II. Activity Questionnaire
 - III. Monitoring Device (e.g. pedometer, FitBit)
 - IV. Other method
- (Please specify other method: _____)
- 2) ***Describe criteria for termination of stimulus: Check all answers that apply.**
- a) *Who determined when stimulus would be terminated?
- I. Researcher
 - II. Study Participant
 - III. Both
 - IV. Neither
- (Please describe: _____)
- b) *Study participant-determined criteria:
- I. Stimulus continued until study participant decided to or asked to stop.
 - II. Based on study-participant symptoms
(Please specify which symptoms: _____)
 - III. Other
(Please describe: _____)
- c) *Researcher-determined criteria:
- I. Heart-rated related: to ____% of maximum heart rate (Define how this was determined)
 - II. Respiratory equivalent ratio (RER) equal to or greater than 1.

PEM-focused Studies CRF

[Study Name/ID pre-filled]

Site Name:

Subject ID:

- III. Duration/ frequency-related:
(Please specify (e.g. minutes, hours, 3 times):_____)
- IV. Stimulus-related (e.g. end of cognitive-fatiguing battery)
(Please specify: _____)
- V. Other:
(Please specify:_____)

3) ***Number and type of symptoms assessed.**

- a) *Were physical fatigue, unrefreshing sleep, muscle pain, and problems of concentration and/or memory examine in this study?
 - Yes
 - No (If No, please specify why these symptoms were not measured:_____)
- b) *If other symptoms were (also) assessed, please describe which ones.

4) ***Timing of outcome measures:**

- a) *Were outcomes measured before, immediately after, 24 hours after, and 7 days after an applied stimulus or after an observational study began?
 - Yes
 - No (If No, please specify why:_____)
- b) *At what other time points were outcomes measured?

5) ***Correlation of Objective Outcome Measures with Subjective Measures:** Were objective outcome measures measured at or around the same time as subjective outcome measures (e.g. patient-reported outcome measures)?

- Yes
- No (If No, please specify why not:_____)

6) ***Outcome measures: What were the outcome measures in this study?**

7) ***Confounding activity and PEM:** Was an objective method used to measure confounding physical activity in this study at any time?

- Yes
 - a) **Describe method of measurement (e.g. equipment utilized)
 - i. Device name
 - 1) Manufacturer
 - 2) Model
 - b) **What was measured (e.g. activity counts, pedometer steps, etc.)
 - c) **When activity was measured
 - ii. Start time for measurement
 - iii. End time for measurementAND (if applicable)

PEM-focused Studies CRF

[Study Name/ID pre-filled]

Site Name:

Subject ID:

- iv. Duration of measurement (specify duration units (e.g., minutes or, how many days) out of a week, how many hours in a day, etc.)

No

PEM-focused Studies CRF Module Instructions

GENERAL INSTRUCTIONS

Aside from these instructions, please read the section Guidance for PEM-focused Studies.

Important Note: All items, including the Yes/No portion of Item 7, are deemed Supplemental-Highly Recommended for PEM-focused studies. Subitems 7a., 7b., and 7c., are designated as Exploratory.

*Element is classified as Supplemental- Highly Recommended.

**Element is classified as Exploratory

SPECIFIC INSTRUCTIONS

- Description of Exertional Stimulus:** “Researcher-applied stimuli” refers to stimuli that are not usually a part of a study participant’s daily activities, e.g. treadmill testing, neuropsychological batteries meant to induce cognitive fatigue, bicycle ergometers. “Study-participant-determined stimuli” refers to activities that participants usually engage in, e.g. walking, driving, household chores, etc.
- Description of Criteria for Termination of Exertional Stimulus:** For researcher-applied stimuli, termination may be decided entirely by the researcher (e.g. 70% of maximum heart rate), entirely by the participants (e.g. volitional fatigue), or by a combination of criteria (e.g. 70% of maximum heart rate or volitional fatigue, whichever endpoint arrives earlier). In the latter case, researchers should check the “both” category for 2a. and describe the criteria in items 2b. and 2c. For study-participant-determined stimuli, researchers have often decided to record activity for a pre-planned time period (e.g. 3 days) and assess activity performed during this time on PEM symptoms. We have left text boxes in anticipation that a variety of study designs may be employed.
- Number and type of symptoms assessed:** Since PEM is an exacerbation of *multiple* symptoms, researchers should examine at least physical fatigue, unrefreshing sleep, muscle pain, and problems of concentration and memory. Researchers are also encouraged to study additional symptoms.
- Timing of outcome measures:** Post-exertional symptoms can start during, immediately after, or hours-days after exposure to a trigger and can last hours, days, weeks, or even 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 past research has concentrated primarily on the time period hours or a up to 3 days after a PEM-inducing trigger. Outcomes should be measured at the very least 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 participant-determined stimuli. We also suggest a time-point past 7 days to capture episodes of long-lasting PEM. Researchers are encouraged to include other time periods in additional to the suggested times.

PEM-focused Studies CRF Module Instructions

5. **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 a participant's condition. If some objective outcome measures were correlated with subjective measures while others were not, please check "No" and provide an answer why this was not done.
6. **Outcome measures:** Outcome measures may be study participant self-reported questionnaires, clinician/ researcher assessments, biomarkers, or a combination of these. Researcher should list the name of standardized instruments used (e.g. Fatigue Severity Scale, DePaul Symptom Questionnaire), the type of biomarker (e.g. cytokine levels, functional MRI), and/or describe the outcome measure in a manner that others can replicate it.
7. **Confounding activity and PEM:** Confounding activity is activity spontaneously engaged in by study participants and not intentionally meant to induce PEM. Because PEM can be delayed and prolonged, accounting for activity before, during, and, sometimes after the planned stimulus is important. In a study with researcher-applied stimuli, confounding activity is activity prior to and/or during the stimuli (e.g. for 2-day cardiopulmonary exercise testing (CPET), activity conducted after the first CPET but before the second CPET is confounding activity). In a study with study-participant-determined stimuli, confounding activity is activity performed prior to when researchers start recording study-participant-determined activity or during times when activity is not being recorded (e.g. if activity is recorded for only 10 hours a day, activity performed during the remaining 14 hours is confounding activity). In some cases, if there is a lag time between the stimuli and measurement of an outcome measure (e.g. blood draw 2 days after a treadmill test or after activity recording has stopped), intervening activity performed after the stimuli may also be confounding activity.

If a physical activity monitor was employed, please see the Exploratory Outcome Measures: Physical Activity table for more details/ guidelines and consider completing items 7a, 7b, and 7c. Objective measures of physical activity are impacted by the equipment used, the types of measurements taken, when activity is measured, and the duration of measurement. Consequently, researchers are encouraged to provide this information in the CRF.

For item 7c., "Start time" and "End time" refer to the first/ last date and time that physical activity monitoring began and ended, respectively. For studies where physical activity monitors were used intermittently, researchers should also complete item 7(c)(iii), specifying the planned duration of monitoring (e.g. 10 hours a day for 3 days, before and for the 24 hours between 2 exercise tests).

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.

- 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).
- 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.

Exploratory Outcome Measures for PEM-Focused Studies: Physical Activity Monitors

As PEM is defined as being precipitated by physical activity, it would be helpful to know what type and level of activity participants are engaged in. Physical activity here refers not only to researcher-applied exercise such as treadmill, bicycle, or ergometer testing but also participant self-determined activity (e.g. activity not prescribed by the researcher but performed before/ during/ after a study). Although physical activity monitors are increasingly used in many areas of research, they are not yet common in the field of ME/CFS. and ME/CFS studies which have used them are of mixed quality (<https://www.ncbi.nlm.nih.gov/pubmed/20943713>). Measurement of physical activity can itself be the primary outcome measure or can serve as the independent variable, e.g. for a study where a putative biomarker is the dependent variable. ME/CFS studies that have employed them have shown, for example, [increases in the number of daily steps](#) taken after treatment with rituximab and [decreases in activity counts](#) during a prescribed walking regimen or [after recent physical activity](#), which may reflect, respectively, improvement in and worsening of PEM.

Physical activity monitors only take into account one precipitant of PEM and other precipitants such as cognitive activity, social engagement, and emotional distress are not recorded. Some participants may also be obligated by, for example economic and social pressures, to participate in work or caregiving activities and consequently, push through symptoms whereas a participant with no or less responsibilities may be able to adjust their activities more flexibly according to their health. Consequently, we suggest that patient-reported diaries and assessment of events accompany objective measures of activity.

References:

1) Examples of uses of activity monitors in physiological studies:

<http://ajpregu.physiology.org/content/early/2017/01/04/ajpregu.00349.2016>

2) Best practices for using physical activity monitors in research (2009 NIH-sponsored forum):

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3543867/>

3) Guideline for reporting accelerometer methods in physical activity intervention studies. Although this is designed for trials, many of the elements described can be applied to observational studies.

<http://bjism.bmj.com/content/early/2016/08/18/bjsports-2015-095947.full>



Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Common Data Elements Subgroup Roster

Post-Exertional Malaise (PEM)

Lily Chu, MD, MSHS (Co-Chair)
Stanford University
Burlingame, CA

Betsy Keller, PhD
Ithaca College
Ithaca, NY

Mary Dimmock (Co-Chair)
Patient Advocate

Anna-Louise Midsem
European ME Alliance

David Cella, PhD
Northwestern University
Evanston, IL

David Patrick, MD
The University of British Columbia
Vancouver, BC

Dane Cook, PhD
University of Wisconsin
Madison, WI

Richard Simpson
European ME Alliance