Guidance for Core PEM Assessment
(DePaul Symptom Questionnaire Subscale)

Availability:	**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. The author, Dr. Leonard Jason, has granted permission for its use and the DSQ is already in use in the field.
Classification:	**Core:** Myalgic encephalomyelitis/Chronic fatigue syndrome (ME/CFS)
Short Description of Instrument:	The "PEM Determination" is a Core CDE instrument to be used across _all_ 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. **Construct measured:** Post-Exertional Malaise (PEM). **Generic vs. disease specific**: Disease Specific. **Means of administration:** Written. Patient self-report plus Researcher/Clinician Evaluation. **Intended respondent:** Study Participant and Researcher/Clinician. **# of items:** 14 **# of subscales and names of sub-scales:** 2 – Post-Exertional Malaise scale of the DSQ and indicator questions **# of items per sub-scale:** 10 for the DSQ and 4 for the indicator questions **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.
Background:	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.

Post-exertional malaise is an abnormal response to minimal amounts of physical or cognitive exertion that is characterized by:

i. 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.
ii. Loss of stamina and/or functional capacity
iii. An onset that can be immediate or delayed after the exertional stimulus by hours, days, or even longer
iv. 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.

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.

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.

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.

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.

Whether the 2-step process is used or not, all studies will use the core PEM CDE which includes the following four components:

1. Patient response to five questions of the PEM subscale of the DePaul Symptom Questionnaire.
   a. Dead, Heavy feeling after starting to exercise
   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 Specify
	Researchers 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:
	    a. Yes
	    b. No
	    c. Inconclusive
	    d. Not Evaluated
	
	Please see the "General Instructions for the CRF" for further details.
	
	Together, these components will produce 14 data elements, 10 for the five questions one each for *DSQ PEM Threshold* and *Global PEM Determination*, and one or two for *PEM* Determination Method *(the second to provide a place to capture other methods if specified).*

Scoring:	**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. Please also see the "General Instructions for the CRF" for further details.
Rationale/ Justification:	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.

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.

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 required to perform and interpret 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 instrument may not accurately capture PEM following stressors unrelated to physical exertion (e.g. cognitive exertion, emotional distress, positional changes, etc.)
- 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).

Reliability: Test-retest: Pearson's correlation coefficients = 0.85 or higher. Internal consistency: Cronbach's alpha = 0.88 [1] and 0.95 [2].

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

- Jason et al has demonstrated good test-retest reliability of the DSQ.

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- 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.

The DSQ calls for an evaluation of symptoms over the last 6 months and this time frame results in the most reliable data.

Other Research using the DSQ PEM Subscale

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.

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