1. **\*Describe the exertional stimulus used to induce PEM. Check all answers that apply.**
2. \*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:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_)

1. **\*Describe criteria for termination of stimulus: Check all answers that apply.**
2. \*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.

☐ 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 all of the symptoms of physical fatigue, unrefreshing sleep, muscle pain, and problems of concentration and memory examined 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:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_)

1. **\*Outcome measures: What were the outcome measures in this study?**
2. \***Confounding activity and PEM:** Was an objective method used to measure confounding physical activity in this study at any time?

☐ Yes

1. \*\*Describe method of measurement (e.g. equipment utilized)
   1. Device name
      1. Manufacturer
      2. Model

b) \*\*What was measured (e.g. activity counts, pedometer steps, etc.)

c) \*\*When activity was measured

* 1. Start time for measurement
  2. End time for measurement

AND (if applicable)

* 1. 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

## **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**

1. **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.
2. **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.
3. **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.
4. **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.
5. **Correlation of Objective Outcome Measures with Subjective Measures:** There is an urgent need for studies where objective outcome measuresare 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 Monitors 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).

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

As PEM can be 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](http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0129898) taken after treatment with rituximab and [decreases in activity counts](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1280928/) during a prescribed walking regimen or [after recent physical activity](https://www.ncbi.nlm.nih.gov/pubmed/22032215), 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.

The suitability of a given monitor for studies in this patient population will need to be evaluated. Certain monitors may be unsuitable, particularly given ME/CFS patients can spend much of their day supine. Please see the Reference below concerning best practices for the use of physical activity monitors in research.

**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://bjsm.bmj.com/content/early/2016/08/18/bjsports-2015-095947.full>