

[...]

Happy Friday,

Attached are my notes/comments.

(Sorry for "dumping" it on you in this way but between my [...] increased health problems and needing a new furnace (ASAP) this was the most expedient way for me to get my comments to you.)

I continue to plug away at the patient/advocate questions and appreciate your help [...].
Sincerely,

[...]

In all subgroup documents-

it would be helpful if the format of all NOCs were the same -

for instance -the section on "short description" should include

construct

generic vs disease specific

means of administration (online/paper, etc)

for all online tests/forms, if a paper (hard copy) format is also available, this should be noted as photo-sensitivity (and sound sensitivity) may preclude some patients from using computers/keyboards. If a save and return option is available, it would be helpful to note that also as depending on how they are feeling, patients may need multiple sessions to complete tests/forms. (The need to use multiple sessions to complete instruments is also useful data)

respondent (patient, caregiver, researcher)*

applicable age range*

number of items

estimated time to complete*

Because of limited cognitive/physical resources, patients may need additional time to complete forms/tests and that could be useful data to capture

It would be helpful to detail that patients may need "recovery" time after completing forms/tests – they likely won't be able to stand up and leave the testing area as quickly as non-ME patients. Being aware of this would be very helpful – especially for those new to the field and would also ensure that patient scheduling allowed for "recovery" buffers.

* Also would be helpful on CRFs

Many subgroups use words such as exertion, exercise, activity almost interchangeably. These terms must be clearly defined and used appropriately throughout all CDE material.

Fatigue is used as a synonym for marked worsening of symptoms following (even minimal) physical or cognitive exertion but which state is really being asked about? (fatigue or PEM)

There MUST be continuous patient/advocate involvement going forward to ensure their involvement in the assessment of all measures developed/modified/etc.

Who is developing the list of terms to be defined in the glossary?

Who is vetting the definitions?

How will uniform use of terms across the CDEs be ensured?

Neuro/Cog/CNS Imaging

It would be helpful for the summary document to include a statement about the applicability (or not) of tests/instruments on severely ill patients.

Baseline/Covariate subgroup

Pediatric demographic and "employment/student history" forms are needed.

Baseline/Covariate subgroup

ME/CFS Adult Employment and Education History CRF should specify it is for those based in the US. (Some terms and concepts apply only to the US)

p. 2 of that form -

#8- If you are disabled from work [awkward construct]

insufficient options under #8

there is a big difference in level of function between option 1 and 2 -should include another option to the effect of Largely homebound or shut in, but can do light housework. This would then require that what is currently option 2 have a phrase added that says cannot do light housework. Before the last option, there could be another that simply is largely bedbound.

#10 The question should be reworded because disability benefits are not given because of a diagnosis but rather because of the level of functional impairment

– needs another option for Not yet eligible (those disabled before the age of 22 who have never been employed, can receive SSDI based on a parent's work history IF the parent is on SSDI, is retired or is deceased.)

Baseline/Covariate subgroup

Medications/other treatments

It could be helpful to be able to list medical devices/implants (insulin pump, pain stim, etc)

(p.1) In the far right column (if med prescribed for ME), the option for "unknown" might be appropriate also.

(p.2) More space is likely needed for the entry on dietary changes

AS FOR CBT and Gradual Exercise Program – neither are proven to be effective treatments for all patients and it should be VERY clear that asking if they have been prescribed is NOT an endorsement of them. This would also be a useful alert to researchers new to the field.

Baseline/Covariate subgroup

Family Health History

Blood disorders should also have option for "Other" and "Specify"

Cardiovascular should have options for "Orthostatic Intolerance", "Raynaud's", and "Other"

Between Cardiovascular and Endocrine there should be a section for ENT

Endocrine section should have option for "Other". Also anorexia nervosa and bulimia show up in this section as well as psychological..... though probably should only be in one section

In Gastrointestinal, IBS should be listed in intestine problems and should there be an option for "Liver" ?

Neurological could include an option for TBI/concussion (though that's not hereditary) and "Other"

Rheumatological should include an option for joint hypermobility syndrome/EDS (type, if known) as well as an option for "Other"

Under Psychological – the option that says "Other type of psychosis" - the term psychosis might make patients uncomfortable. (and from what I understand, psychosis generally refers to a "break with reality". Perhaps it'd be better to just have an option for "Other"

Under Other Conditions -

"Medically unexplained syndromes" is an inappropriate phrase to include here. While denying the physiological evidence about ME, several psych-oriented "researchers" have tried to assert that ME is actually "Medically Unexplained Symptoms/Syndrome" and have caused harm and distress in the community.

http://www.rcpsych.ac.uk/pdf/CHECKED%20MUS%20Guidance_A4_4pp_6.pdf

<https://www.jcpmh.info/wp-content/uploads/jcpmh-mus-guide.pdf>

Medically unexplained symptoms (MUS) is the term used to address disorders where physical **symptoms** have no **medical** explanation. Currently, most patients with general MUS fit the diagnostic criteria for 'undifferentiated somatoform disorder' (DSM-IV, 300.82; **ICD-10**, F45.1).

https://www.google.com/imgres?imgurl=http://scielo.isciii.es/img/revistas/ejpen/v21n1/rosendaltable2.jpg&imgrefurl=http://scielo.isciii.es/scielo.php?script%3Dsci_arttext%26pid%3DS0213-61632007000100004&h=635&w=750&tbnid=6UcoCunJQu9raM:&tbnh=160&tbnw=188&usg=__LGvzFXiPSdo56piATSJO5FMM_IE%3D&vet=1&docid=1wwwLMuHlzkOnM&sa=X&ved=0ahUKEwjS0_KE4-TXAhWBk-AKHAYAKD28Q9QEIKzAA

<https://academic.oup.com/ocmed/article/62/1/73/1486484>

While the etiology of the illnesses listed in this section may be unknown, they are physiological in nature and referring to them by a term that has so much psych baggage is not a good idea.

There are 4 gyn options – what about options re male reproductive health?

In "Birth, familial or genetic defects" consider changing "defects" to "conditions" and move Ehlers-Danlos to rheumatological or have an entry (here and in past and comorbid conditions) for connective tissue disorders.

Should pubertal status of family members be asked about?

Baseline/Covariate subgroup

Past and Current Medical Conditions

Patient age on the form would be helpful particularly as some of the questions – especially about reproductive status – do not apply to patients who have not yet reached puberty.

It would be good to consider adding options about pubertal status.

Under Cardiovascular

should Raynaud's be added?

Orthostatic Intolerance or POTS could also have something to the effect of "(history of fainting)"

(as with the previously mentioned form)

Under Psychological – the option that says "Other type of psychosis" - the term psychosis might make patients uncomfortable. (and from what I understand, psychosis generally refers to a "break with reality". Perhaps it'd be better to just have an option for "Other"

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<https://academic.oup.com/ocmed/article/62/1/73/1486484>

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Baseline/Covariate subgroup

Symptom Checklist – Form A (CDC form for History of Present Illness)

A concern with all forms asking about things in the past is that people may not remember what normal is IF they ever knew – as in the case of an adult who became ill as a child and is asked to compare their current activity level/health to pre-illness. As people age, their activity levels (cognitive and physical) change and what is normal for (example) an 8 year old is not necessarily normal for a 46 year old.

Even remembering what normal/healthy felt like is subjective. (Are we wistfully remembering what we were once able to do? How accurately do we remember how many pages per minute we were able to read or if we were really able to track 3 conversations at once as our friends talked around us?)

Fatigue, fatiguing, fatigued, substantially – are some of the terms that need to be clarified.

It would be helpful to have spaces for name, age, etc on the form. For ped patients, a parent/caregiver may need to fill the form out. Specifying this on the form may be helpful.

I am not sure this form captures the duration of post-exertional exacerbation of symptoms as expressed by the PEM subgroups. Nor does it refer to PEM by a name recognized by researchers/clinicians/patients but instead seems to refer to it as “fatigue after exertion” which is not what PEM is and is not a phrase that is typically used.

It does not ask about lightheadedness/fainting/OI symptoms.

Sleep changes in adolescents/teens are part of the maturation process but questions here don't provide for those changes. (So applicability of this form for ped patients?)

Grouping symptoms by body part might be helpful -for instance it seems GI symptoms are interspersed in several places with things like muscle pain, headache, etc between diarrhea and nausea.

C.1e and C.1f Would these be better understood if they instead asked if the “fatigue, tiredness or exhaustion” felt was different from previous ill-health feelings (for instance from flu, cancer, pneumonia, etc)?

C.1g -would “gradually” be more easily understood than “slowly” because, how slow is slowly? 3 months, 6 years?

Fatigue after Exertion

C.5 does duration asked about here (“at least one day”) align with PEM group?

Does this refer to cognitive exertion as well as physical exertion? Does it refer to cognitive “fatigue” as well as physical following exertion?

Fever

C.8 anecdotally at least, patients often report lower than usual body temp as their “normal” so it might be helpful to get info on that.

Sleeping problems

How does this section align with the sleep subgroup recommendations?

This section asks about sleeping through the night which does might confuse patients whose illness experience has them in day/night reversal.

This section does not ask about pre-illness sleep or naps and does not take into account the changes in adolescent sleep patterns.

Stomach pain or abdominal pain

Does this also refer to cramping?

Sensitivity to Light

What about sensitivity to sounds/smells/touch (which are also often part of patient's symptoms)?

Baseline/Covariate subgroup

Questions from the DePaul Symptom Questionnaire(DSQ)

[numbering begins with #13.... that could be very confusing. People may think they misplaced/did not receive questions 1-12]

Parents/caregivers may have to fill this out for young patients and those with very limited cognitive resources. A statement to this effect would be useful on this (and many other forms/instruments).

Terms such as fatigue, energy, exercise, activity, need to be clearly explained and all terms that overlap with materials from other groups must align with each other.

The DSQ has few questions that ask about OI and terms such as dizziness (which could be from an inner ear problem or vertigo or) don't truly capture the sensations of OI.

Tiredness/exhaustion/drained etc occur after cognitive exertion as well as physical exertion and cognitive exertion can be further impaired after cognitive and/or physical exertion. These concepts should be included in questions asked.

#19 – asks if person is refreshed when they wake in the morning but this does not take into account those with day/night reversal. And patients may not understand if the question is about how someone feels in the morning or how one feels upon waking after one's extended sleep , be it day, night or afternoon.

#23 asks about waking early in the morning (again, this does not account for those with day/night reversal) but does not specify if this means without being about to get back to sleep or simply waking for a while during one's extended sleep-time.

#34/35 ask about sensitivity to light and sound but often patients are sensitive to smells and touch also. Why is #66 so far from light and sound sensitivity? Are there any questions on sensitivity to touch?

#37 asks about paying attention for a long time – it'd be helpful to clarify what "long" is as for some patients that can be 5 minutes, for others it could mean 60 minutes....

#40-I assume that ability to focus refers to cognitive focus as opposed to visual focus but should this be made clearer for patients so as to minimize cognitive exertion when completing this?

#s50/51 ask about dizziness (which can occur in conditions other than OI)/fainting/irregular heartbeats -this area would benefit from additional questions about lightheadedness, change in ability to focus depending on whether laying down, sitting or standing upright as well as asking about rapid heartbeat unrelated to exertion.

#55 asks about nightsweats – does this refer to sweating at night independent of sleep or sweating during sleep whether it be day(for those with day/night reversal) or night ?

#71 asks about prolonged fatigue following exertion but might be better understood as prolonged exacerbation of symptoms following exertion.

#78 -it might be helpful for include an option that allows for PEM as worsening of symptoms but a return to baseline symptoms as opposed to a period with “no” symptoms

#79 might be helpful to include an option for partially bedridden

PEM

Has the current accuracy of FitBits been verified? (A few years ago they did not seem to accurately capture movement, sleep.)

Should recommendations include the development of measures that capture cognitive PEM as well as the impact of PEM on cognitive function?

Cognitive stimulus measures vary by age which means that an instrument used in studying pediatric patients would be different than those used in adult populations. Has this been adequately addressed in the subgroup’s recommendations?

I think there could be benefit in documenting the time elapsed from completion/termination of PEM stimulus to the time when the patient is able to sit, stand, and or remove self (or be removed) from the study area.

p.4

“It should also be noted that almost all PEM studies have been based on adults and the DSQ has not been tested in children.” Is there a therefore after this? (as in, therefore the DSQ should be validated in children and/or there should be PEM studies on ped patients?)

p,6

#6 Unmet needs

Ascertaining if there are differences between cognitive induced PEM and physically induced PEM.

p.12

reDSQ questions –

a) distinction between exertion, activity and exercise must be very clear.

d) minimum exercise – does this refer to cognitive exertion as well as physical or just physical?

p.14

Paragraph beginning “In its report....””...the expertise required to perform [and interpret] the test.”

p.18

Core PEM Assessment CRF

“Dead, heavy feeling after starting to exercise” - is this understood to be that particular episode of exertion/activity/exercise (which term is most appropriate here?) or an exertion/exercise (which term is most appropriate here?)program?

p.19

#3-5

do these refer to cognitive as well as physical exertion?

p.27

As the sentence is currently written, it could be understood as PEM is only triggered by physical activity. Would it be helpful to clarify the first sentence on this page by saying (something to the effect of) "This study area is examining PEM as it is precipitated by physical activity". –

p.30

#3

Would it be helpful to clarify that the end of a stimulus may also be the inability of the participants to complete the cognitively fatiguing task?

PEM-focused CDE CRF (draft)

p.2

#2

re the question about heart rate and %of max heart rate – does this apply to patients who have elevated heart rates at all times?

Last page (they aren't #ed)

paragraph that continues from previous page – says outcomes should be measured at least at baseline, at 24 hours and at 7 days.

BUT p.31 of the subgroup document says outcomes should include measurement at 21 days also..

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 three different time points: at baseline (time point 0, before the stimulus is applied), at 24 hours, and at 7 days after the applied stimulus or after the study has started for ecological studies. Ideally, studies will also include a time point out to 21 days to capture potentially longer-duration PEM.

QOL/Functional Status/Activity

The Bell and Karnovksy scales both use numbers from 0-100 but the gradations are so different. (just a comment – though it could be that if both were administered to patients they might be confused)

Under specific needs or gaps

Are there gaps in assessment measures applicable to adult ME patients and those applicable to pediatric ME patients?

Does the subgroup anticipate that one instrument differentiating between physical and cognitive function would apply to adult AND ped patients?

Age range, time to administer, who fills out the instrument, is instrument online/paper should be part of short description in all NOCs.

On CPET form(p.29) there is an option for "sex". It might be helpful to change that to gender.

p.30

There should be a way to document how much time elapsed after completing the CPET testing before the participant was able to become upright and leave the testing area and/or facility.

p.32

The entry for "working" should also have "studying" for young patients.

Question #2

To me there is a big enough difference between these two activity levels that an option in between the two would be useful.

- am shut-in: I can walk around the house but cannot even do light housework or its equivalent.
- can work only part-time at my work or on family responsibilities.

pp.32-33

#5

it might be helpful for include an option that allows for PEM as worsening of symptoms but a return to baseline symptoms as opposed to a period with "no" symptoms

p.33

#7

"tired" may not be the best understood word to use. New researchers may not understand how different "tired" in ME patients is from what it is in other populations. Patients with ME also tend to dislike "tired" as it is not descriptive of their experience.

Sleep subgroups

#3 summary recommendations chart should include a column to note if instrument is for all, ped or adult populations.

#4 Comparison to other ME/cfs standards

in the response, the name of the article needs to be corrected. (see reference for correct name)

Sleep Focused CRF

is the intended study done in-home or at a sleep center?

Question #3 says medication log must be completed but I do not find it. Did the group intend for there to be one included?

Sleep Questions for all studies CRF

says medication log must be completed but I do not find it. Did the group intend for there to be one included?

NHANES Questions: [what is NHANES?]

#1 Do you have trouble falling asleep? "trouble" as defined as taking how long to fall asleep? 5 minutes, 2 hours? Is the question subjective or is there a minimum amount of time after which it is considered "trouble"?

#2 “trouble” getting back to sleep – is there an amount of time after which one is considered to have trouble getting back to sleep?

#3 “in the morning” - how does this apply to people with day/night reversal? (Can wording be changed to include them?)

#4 - “feel unrested during the day” - how does this apply to people with day/night reversal? (Can wording be changed to include them?)

[...]

Dear [...],

We recommend adding the following:

CPET provides an objective measure of fatigue via the respiratory exchange ratio (RER), which is the ratio of carbon dioxide production to oxygen consumption. This measure is unavailable with conventional exercise testing where the degree of effort or fatigue is estimated from subjective ratings of perceived exhaustion (RPE), the percentage of predicted maximal heart rate achieved during the test, and through tester opinion. Maximal heart rate has a high degree of individual variability and can be affected by both medication and disease pathology.

Best,

[...]

[...]

Hi,

Please advise if there is somewhere else to submit my comments. I'm just a patient, live far away, and am not familiar with your procedures.

For the immune module:

1) There aren't any drugs for hereditary hemochromatosis. The treatment is phlebotomy. You might ask how frequently a patient gets these.

2) In the section on infections - the Other box is too small (I have 7 infections). In addition to those listed, infections that many of us have include HSV1 and 2, HHV6 and 7, Parvovirus B19, Toxoplasmosis, Cocksackie, and Enteroviruses, as well as atypical acellular pneumonias like Chlamydia Pneumoniae and Mycoplasma Pneumoniae.

3) Many of us have autoimmune antibodies that have been identified, such as adrenergic, muscarinic, NMDA, paraneoplastic, etc. [...] of the newly formed Stanford ME/CFS Center of

Excellence and his private practice, [...], could give you a good list of these. (Some of these antibodies seem to be behind our postural orthostatic tachycardia syndrome, orthostatic intolerance, or neurological symptoms.)

4) There is a subset of patients with mold exposure as the root cause. It is a treatable problem and many have been cured.

Thank you for taking my input and getting it to the right people.

Sincerely,

[...]

[...]

Dear Sirs, A longshot idea here. What if we could use electricity to treat Myalgic Encephalomyelitis/Chronic Fatigue syndrome? That is, what if we placed a naked CFS patient atop a stainless steel examination table, that is electrically grounded, and create an overhead moving shuttle, with a curtain of hanging stainless steel chains (it all has to be stainless steel for disinfections to sterilize all of this gear, free of any diseases, after each use in this application), and we pass this chain curtain over the CFS patient's entire body, while passing a LOW amplitude, but HIGH voltage, direct current charge, through the chains and through ALL of the CFS patient's body, and into the grounded table? PERHAPS this 'electric massage' will kill off WHATEVER is causing the Chronic Fatigue Syndrome disease. Remember, Lyme Disease is caused by a parasite, so maybe CFS is caused by some as yet undiscovered parasitic organism as well. Also, perhaps this 'electric massage' can somehow jumpstart the CFS patient's immune system, charge it up with energy perhaps, to enable such patients to fight this disease better.

That covers it. Best Regards, [...]

[...]

Hi [...]

I added one more item to this comments form, and am the phone conference line now; were we going to talk at your 10 am today?

[...]

Hi [...]

I have placed some comments on the attached form, and as I have gone through all the documents, it is clear that for youth, there are some fundamental areas that are not covered. I am [...], and yes, it would be great to speak with you next week about these concerns. Clearly, adult measures are nicely covered,

but there are some real gaps for kids that need to be thought through.

I can call you next Wed at 10 your time, and discuss this issue with you in more detail. Until then, you

can see from my attachment a few of the issues that could profit from our attention.

[...]

Subgroup	CDE, Case Report Form or Measure	Suggested Change	Rationale
Quality of life	Child Health Questionnaire	Needs to be required to assess functional status in children	The parent and child or adolescent can complete the Child Health Questionnaire (CHQ; Landgraf, Abetz, & Ware, 1996), an instrument that assesses physical and psychosocial well-being. The instrument has both an 87-item child form (CHQ-CF87) and a 50-item parent form (CHQ-PF50). The scales measured by both forms include physical functioning, role/social (emotional, behavioral, physical), bodily pain, general health perceptions, and self-esteem. The parent form has two additional scales, "Parent Impact-Emotional" and "Parent Impact-Time." Internal consistency reliability coefficients are good for the CHQ (0.84 for the child form; ranging from 0.80 to 0.88 for the parent form, depending upon the parents' SES). Furthermore, the CHQ evidences acceptable validity. Discriminant validity of the subscales is excellent, as the scales can discriminate children with clinically defined conditions from a control sample (Landgraf et al., 1996). Finally, there are parent and child rated norms available for each subscale, and the CHQ has been found reliable down to age 5 (Drotar, Schwartz, Palermo, & Burant, 2006).
fatigue	Modifiable Activities Questionnaire (MAQ)	Should be required for studies with children	Physical activity during both productive and leisure time, as well as inactivity, can be assessed within six months prior to the time of the full evaluation using the MAQ (Kriska, 1997). The MAQ was adapted from the Minnesota Leisure Time Activity survey (Folsom et al., 1985) in order to create an assessment of physical activity, and can be used for youth samples (Aaron et al., 1995). The MAQ employs an approach considered to be the standard for self-report of physical activity in epidemiological studies. It has adequate test-retest reliability, correlates with objective measures of physical fitness (Aaron et al., 1995; Kriska, 1990; Kriska, 1997) and has been used down to age 5 (Andreacci et al., 2004; Hussey, Gormley, & Bell, 2001, Murray, Brahler, Baer, & Marottaour, 2003).
baseline	School Attendance	Should be required for studies with children	The number of days attending school over the week prior should be recorded, as well as the number of hours each day that the child was able to attend school. If the participant is home schooled, the number of hours of instruction per day and number of days receiving instruction for that week should be recorded. Parents should provide these data, as their estimates are reliable (Fein et al., 1999).
baseline	Pediatric ME/CFS screening questionnaire	should be supplemental for children	The <i>Pediatric ME/CFS Screening Questionnaire</i> can be used to screen for ME/CFS-like profiles among children and adolescents. This screening questionnaire consists of three parts. First, there are questions designed to determine if any of the children or teenagers (ages 8-20 years) in the household are experiencing significant fatigue.

			The second part assesses whether any of the children are experiencing disruption in their school activities or performance due to fatigue or cognitive difficulties. These initial questions are broad in order to cast a wide net to increase sensitivity and detect all possible cases of ME/CFS. The third part of the questionnaire presents a list of ME/CFS-related symptoms in children proposed by Bell (1995), Jason et al. (2006), and others (Fukuda et al., 1994; IOM, 2015; Carruthers et al., 2003; Jason et al., 2010).
baseline	Three questions were left off the DePaul Symptom Questionnaire for Baseline group		
		97. Since the onset of your problems with fatigue/energy, have your symptoms caused a 50% or greater reduction in your activity level?	
		q Yes q No	
		98. Do you experience frequent viral infections with prolonged recovery periods?	
		q Yes q No	
		99. Are you intolerant of extremes of temperatures (when it is extremely hot or cold)?	
		q Yes q No	

[...]

Our all body function controlled by electric system. Our body controlled 13 major control system.

If nerves control system blocked, we enter in mental disorder.
 If digest control system blocked, we enter chronic digest disease. If all control system blocked, we have many ill.
 If we have many ill, we call chronic fatigue syndrome.

The pathogenic source(invisible) may many types

1 Water veins(under river) electromagnetic radiation above bed or chair 2 .

High uric acid level

3. stress

4. bacterial metabolite

5. accident induced molecules

6, pregnancy (may blocked some control system for emergency metabolic change)

7. toxic bra, cosmetic, glass, accessory, bedding

8. toxic food

9. negativecharge 10

etc.

cure the mental disorder chronic ill chronic fatigue sysdrome

1. remove the pathogenic source(it need special inspiration)

2. Body electric flow tune up

The disease may instant fix(may 10 minutes -several days) [...]

[...]

My name is [...] and I live in [...].

I was having so many weird symptoms, no one Doctor or Specialist knew what to do with me.

When I started Blacking out and/or Fainting at my Private Practice on [...], I had to close my Practice and start seeing Doctors full time for test after test.

A friend drove me around, so I wouldn't have to deal with parking and walking.

Finally one Disease Specialist told me if I could bring in written justification for a test, he'd order it. After 2 years and many tests later, I was diagnosed with Chronic Fatigue Syndrome/Fibromyalgia.

I took these findings to a Disability Attorney.

Possible precursors:

1. When I was 5 yrs. old my parents though I was getting Polio. My Temp was very high and I couldn't turn my head.

A Church friend of Dad's asked them to meet him at his chiropractic office. I only remember—"listen to the popcorn" as he jerked my head all around.

I was told he worked on me all night. My parents believed he saved my life.

2. When I was 16 yrs. old, I had a Brain event that left my left side totally paralyzed from head to toe.

MRI's hadn't been invented yet, so my Doctor told my parent's I'd had an occlusion—vessel in front of brain collapses, cutting off oxygen to the Brain.

My best friend at the time offered to take me to physical and occupational rehabilitation.

The school Nurse called my parents and told them I might qualify for Voc. Rehab. as a cripple. My parents took me to Voc. Rehab. and we were told I could get College Coverage of everything.

My mother didn't know if I'd be able to learn, so she told me to take 2 classes over the summer at [...]. She also taught me a condensing process to turn sentences into a single letter and letters into paragraphs.

My parents said I had to go to a Baptist College, so I picked the one farthest from home.

Here was my chance to be whoever I wanted.

I only had a very slight gait when I walked and I could use my hand but not my fingers. I became an expert at disguising my left fingers.

After trying to be invisible through HS, I was chosen along with 14 other freshmen girls as best looking new arrivals.

From this group of girls, 4 of us were chosen to run for [...]. (It was [...] in [...].) My Mother loved the Newspaper pictures I'd send her.

I was photographed with the Football Quarter Back pinning a corsage on me. The picture was used in the [...] magazine.

Finally, I was experiencing what I'd missed out on in HS. I left after 2 years because girls had rules for everything, but boys had none.

I worked part time at a call center and went to [...] full time. I moved in with 3 girls looking for a forth to help with rent.

I still didn't have use of my left hand, but wasn't really aware of other symptoms. Getting away from my abusive mother, I was thinking for myself for the first time. She even said I had to be a teacher if I wanted a job when I graduated.

I had wanted to be a Social Worker.

I graduated and was hired at the [...] working with Alcoholics and drug addicts.

A co-worker said a brand new group had come to town and built a high dollar Treatment Center called [...]. He said he thought I could get hired and gave me the information.

I was hired because of all the Mental Health Books I'd read and my gift for BS.

Here I am at 69 years old and my CFS/ME has gotten worse with age. I'm still in [...]. which doesn't have cutting edge Scientists.

I see a Neurologist every 6 months—more if needed.

Even the high dose Meds. he has me on don't put and keep me asleep.

It takes my brain 4 hours after taking the high dose Meds. to even feel tired.

Then I'm up with Interstitial Cystitis at least 3 times a night and have to try to accumulate as much sleep as can. I have 3 Disabilities:

1. Chronic Fatigue Syndrome
2. Fibromyalgia
3. Secondary Depression
4. Over the last 3 years I've shown 7 new Diseases in my blood work. 3 require a specific diet but none are the same, so I stick with the IC diet.

I never leave the house except with my dog in the car to the store. I've had [...] for 9 years.

The only living person I know in the USA is my friend down in [...]. who can't dive to [...] anymore due to her Spine. Three surgeries—none left.

Social me has become a hermit because talking to people wears me out.

I just found out [...] has an enlarged heart and her lungs fill up with fluid. The Vet gave her 6 months to, at most, 2 years.

She's my fourth and last dog.

I wouldn't have the stamina to start over with a puppy.

I tear up every time I type or say those words about [...]. For the first time they'll be no beating heart to love.

I will be so lonely.
I'm with her all day every

day. Sincerely,

[...]

[...]

1.) First let me explain. I am 62 years old and was diagnosed by a seminal ME/CFS researcher and physician at [...] over 25 years ago. Quite sure he is no longer a researcher and most likely not among the living.

2.) I am professional researcher working from bed on my computer due to ME. I research and evaluate . . .

PSYCHOLOGICAL HEALTH (not the archaic term of mental health, so please delete that term, MH, in your forms) and TBI military clinical and medical programs. Previously an educator, trainer, speaker, psychological health (PH) therapist/clinician and school psychologist.

3.) Have tried most therapies available and some not so available. In desperation, with the lack of proven research, and with what little that works and, try many things you would otherwise cringe at doing.

4.) Research limitations:
The comment Excel spreadsheet could be daunting to those who are not familiar with the Excel processes. That may include many. Thus putting research limitations on your gold standard study of medical research.

5.)
Please allow me to expound on the fact that with ME there are a plethora of gradations and an excess of varying time spans where those gradations greatly fluctuate. Basically it changes for most of us from day to day and within the day. I have lived for the past two years confined to my bed, but luckily the last two months I can walk and even make breakfast some days. Taking baths daily? Not so much. But you just never know. Thus why .

..

6.) Why many ME patients cannot get SSI because of these fluctuations. Also, as you probably know, with ME symptoms you need a veteran and well paid attorney (heavy finances) to even apply for SSI, much less receive SSI. My brother works for SS and is told to automatically reject ME applications on the first THREE attempts. (No, I don't get SSI.) Can you imagine what this does to the ME patient emotionally and physically fatiguing and financially draining? I would add to your surveys these . . .

7.) EDITS:

**SSI:
HOW MANY TIMES HAVE YOU APPLIED FOR SSI? and HOW MANY TIMES
HAVE YOU BEEN DENIED SS?**

Aside commentary: So, I would surmise there would many more receiving SSI if we did not have such a thwarting, financially padded and biased SS system. My brother works for SS and is told to reject the first THREE attempts for applying for ME SSI. This may be a factor in why several ME patients have suicidal ideation and have committed suicide. Hmm suicide? I did not see any mention of suicide on these forms?

SUICIDE: HOW MANY TIMES

HAVE YOU HAD SUICIDAL THOUGHTS, IDEATIONS, PLANS, ATTEMPTS?

Suggest these be added.

Aside commentary: NIH, CDC, SAMHSA, Congress, News media, etc. might be interested that you did or did not do this data collection on suicide. It appears egregious to omit when most ME patients have co-morbidities of depression and anxiety disorders and therefore, at a great risk for suicide. Don't you agree? You might want to check the stats on those ME patients who have already committed suicide, then check with their families to find out why. My guess would be it was the ramifications of this disease.

change to either

AMERICAN, please add **ETHNICITY/RACE**: Omit American Indian and

NATIVE/INDIGENOUS

INDIAN as an

ethnicity (as one who descend from the country India, as there are ME sufferers from Indian descent). Change . . .

WHITE/CAUCASIAN. Many African Americans do not like to be referred to as Black, and many from European descent do not like being referred to as White. Also, there are great many

JEWISH or from HEBREW DESCENT that have as many genetic anomalies (susceptible or impervious to lesser known disorders/conditions/diseases) as the Native/Indigenous American. (Yes, I have researched this)

HEARING: add **TINNITUS**

ADHD (not just ADD)

FATIGUE: add **HAS YOUR FATIGUE LIMITED YOUR ABILITY TO EXERCISE-EVEN MILD WALKING?**

BRAIN FOG: add **HOW SEVERE IS YOUR BRAIN FOG or ABILITY TO REMEMBER?, IS IT SEVERAL TIMES MONTH, WEEK, DAY, NONE?**

TIME FRAMES: Ask not only how many times this month, but change to **HOW MANY TIMES THIS MONTH, IN LAST THREE, SIX**

AND 12 MONTHS. ME can greatly fluctuate between months.

SENSITIVITIES: add to **NOISE and SOUNDS, DO YOU STARTLE EASILY?** change bright light to **LIGHT**, add **CHEMICALS/PERFUMES**

MEDICINES: **DO YOU HAVE TO HAVE MEDICINES TITRED or START WITH LITTLE AMOUNTS AND SLOWLY INCREASE?**

THYROID: HAVE YOU BEEN TESTED FOR THYROID ISSUES? DO YOU HAVE HIGH THYROID?, DO YOU HAVE LOW THYROID?, IS YOUR THROID DIFFICULT TO REGULATE (UP AND DOWN)?, WHAT THYROID MEDICATION(S) DO YOU TAKE?, DOSEAGE?, HOW OFTEN?, DOES IT SEEM TO HELP WITH THE ME?

RA: please note about 20% of people who have RA were blood tested with false negative. Some of the worse cases of RA come back negative on blood tests. Only way RA can be definitely tested is with the BONE SCAN.

FEMALES: OVARIAN CYSTS/FIBROIDS?, MENSURAL CRAMPS?, OTHER GYNOCOLOGICAL ISSUES?, DO/DID YOU USE BIRTH CONTROL? FOR WHAT REASONS? WHAT TYPE? HOW LONG? DO YOU TAKE HORMONE REPLACEMENT (HRT)? FOR WHAT REASON? WHAT TYPE? HOW MUCH, IF KNOWN percentages of ESTRODIAL, PROGESTERONE, TESTOSTERONE? HOW LONG? WHEN DID YOUR MENSES or PERIODS stop? DID YOU HAVE A HYSTERECTOMY? WERE OVARIES LEFT OR TAKEN? WHY DID YOU HAVE A HYSTERECTOMY?

MALES: DO YOU SUSPECT YOU HAVE LOW TESTOSTERONE? HAVE YOU BEEN TESTED FOR LOW TESTOSTERONE? ARE YOU TAKING TESTOSTERONE? If, so WHAT? HOW OFTEN? HOW

MUCH? Please note recent fibromyalgia research suggests that low levels of testosterone seem to increase pain. We know stress increases levels of cortisol increase pain.

THREE OVERALL QUESTIONS to add: 1.) WHAT HAVE YOU TRIED THAT WORKS? 2.) WHAT HAVE YOU TRIED THAT DID NOT WORK? 3.) IF KNOWN, EXPLAIN WHY IT WORKED OR DID NOT WORK?

Please, please, please Omit: the word PSYCHOSIS as this is an especially inflamatory word (like mentally retarded), for many suffering from PH illnesses. Suggest changing to PSYCHOLOGIAL HEALTH illnesses/disorders/conditions

KNOW YOUR AUDIENCE: When dealing with patients with ME please understand we are not functioning on all four cylinders, if we even have THAT many, and the severity levels fluctuate. If possible when filling out forms or interviews it would be helpful to have a **spouse, close friend or significant** with the ME patient, as many times they may have a better perspective on what we (ME patients) can and can not do. Denial sometimes is a great promoter for patients coping with irratic health issues that physicians/reserachers have no answers. Also, the education level and information levels greatly vary. You may ask do you have "tinnitus," and the patient does not know what that means. They might say NO, but if you ask "Do you have tinnitus or ringing in your ears or it sounds like crickets chirping in your ears?" then they might say YES. So, please **clarify medical terms** as you query patients

Dear Sir/Madame

I am an ME patient. It is crucial that researchers use consistent criteria when recruiting for ME/CFS studies. The Fukuda criteria is far too broad and should be cast aside for good.

The cardinal symptom and most disabling symptom of ME/CFS is PEM or post exertional malaise.

This MUST be present in all patients participating in research studies.

The ICC or IOM criteria are suitable as pem is mandatory. The ICC is excellent.

Please ensure that appropriate criteria is being used, otherwise it's money down the drain and patients are left to die.

Please move this forward quickly, ME patients are suffering, years wither away while we wait and wait. So many lives destroyed, it is time to intervene and find answers as quickly as possible.

Kind regards

[...]

[...]

Dear Sir/Madame

I am an ME patient. It is crucial that researchers use consistent criteria when recruiting for ME/CFS studies. The Fukuda criteria is far too broad and should be cast aside permanently.

The cardinal and most disabling symptom of ME/CFS is PEM or post exertional malaise. This MUST be present in all patients participating in research studies.

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Kind regards

[...]

[...]

Thank You.

I look forward to the ME/CFS information you send me.

I'm too poor on Disability income of \$914 a month to make contributions. I truly regret that.

I appreciate you writing me back. I could have said a lot more, but tried to keep it short.

For example: My mother beat me daily. She got on top of me when I was 5 yrs. holding a butcher knife at my throat saying she was going to kill me if I didn't tell her who put the tiny hole in the dining room table. She had me lean against the wall and whipped my back legs with coat hangers until they bled.

My brother raped me when I was 22 yrs. old. My Southern Baptist Evangelical Father stayed gone directing the Music and playing his trumpet at revivals.

I later understood when I became a Therapist that she had Manic-Depression.

I grew up terrified. Growing up terrified could also be a precursor to CFE/ME. Love to all at ME/CFS,

Sincerely, [...]

[...]

Thank you so much for your recognition – and PUBLICATION! – OF THIS major health problem. I am reminded of the “Golden Girls” segment in which the physician states that doctors ignore the problem because “they can’t see it in their test tubes just yet”.

I have been so sick, for so long, and doctors have been negligently stupid (misdiagnosis as bad as possible).

Thank you, and please continue with your good work. [...]

[...]

Hello. My name is [...] and I've had ME/CFS for over 8 years now. I saw on the [...] forum that you are asking for patients to contribute to the conversations on how PEM is to be defined for research studies, and am emailing to ask how I can add my voice to this discussion.

Do you want comments shared just via email, or is there a specific form/survey or questionnaire you are sending out to glean the required information from us?

I am also an advocate working with children and families living with ME/CFS as well as having it myself, and as a community we are very keen to support the real science happening on our behalf, so if we can contribute in any way to your research we would love to do so.

We are eternally grateful for the valuable work you are doing to try and help ensure the research in this field is of the highest quality and it is extremely reassuring to know that patients such as ourselves are finally being included in these processes.

I look forward to hearing from you with regards to sharing our thoughts on PEM and its definitions. This is something that is regularly discussed and explored in our patient workshops, so we feel we could collectively contribute to this conversation.

All the best, [...]

[...]

In my ME patient experience,
PEM is happening when minor exertion produces the following symptoms:

IMMEDIATE
.Pain
.Air hunger
.Trembling

- .Racing heart
- .Dizziness/faintness
- .Stumbling
- .Muscle weakness
- .Muscle cramping
- .Energy exhaustion
- .Need to stop/rest now

POST EXERTION

- .Undue muscle cramping
- .exhaustion
- .for days

Sincerely,

[...]

[...]

I am writing as a patient to comment on your proposed CDE regarding post exertional malaise (PEM) in myalgic encephalomyelitis (ME/CFS).

As background, I was diagnosed and am being treated by a top ME/CFS specialist at the [...]. I'm in the mild to moderate category, where my energy varies. I am able to work about 10 hours a week and I can do some exercise, mainly weight lifting, stretching, and slow walking, as cardio exercise is impossible due to my condition. I still spend most of the remainder of my life on the couch or in bed, resting from exertion as my body is telling me not to do more or I'll pay for any additional effort with PEM.

I experience PEM after I've overdone it with too much intensity or quantity of physical effort, if I've had to focus intently on something at work, or I've been under any emotional duress (which can be being very happy about something, as well as feeling anxious, stressed, or angry). Typically this PEM will last 1-4 days.

Your 28 page document is very impressive. Most of it looks very well thought out and it's comprehensive.

However, the choice of the DSQ symptom questionnaire is problematic. It may be the only questionnaire that's been used in studies, but relying on it would serve up a skewed population and give false results. It would do the ME/CFS community a grave disservice.

As a patient, I likely wouldn't score high enough on the DSQ to qualify for any studies, even though PEM (and limiting my activities to avoid PEM) is a significant factor preventing me from having a normal life.

The DSQ asks for frequency and severity in the past 6 months, which is a problem if a patient has been trying NOT to provoke PEM. If we are careful, many of us try to actively avoid PEM, and can be fairly successful, so provoking PEM is an exception, rather than the rule.

And for those of us who are less ill than others, our PEM, while still significant and disabling, preventing us from normal activities and work, is typically less severe than that of the severely ill ME/CFS patient.

We who are mildly to moderately ill are still quite sick, and are struggling to keep our jobs, be part of our families, and attempting to do normal activities, frequently at 60-70% of normal, so we're 30-40%

impaired. We have the best chance of beating this illness, better than the severely ill, and PEM episodes can set us back, reversing progress we've made in treatment.

There is great value in studying the PEM if mild to moderately ill patients to find ways of reducing it, avoiding it, and keeping us moving forward in our treatment.

The DSQ assumes we can't exercise at all, and that PEM will be provoked after starting exercise or a minimal quantity of exercise. This is not the case at all. Many of us can do a careful amount of exercise without triggering PEM - it is only after going over some arbitrary threshold that PEM is triggered, and that PEM can be substantial. We learn to monitor heart rate and energy levels and respond to these cues in planning our exercise.

Again, those of us who can exercise some are still quite ill, but less so than the severely ill, and we have hope of recovery. Having more insight into managing and monitoring PEM with exercise (and other types of physical activity) can provide insight to researchers.

Similarly, many of us can make a minimal mental effort just fine. It is only after reaching some threshold of cognitive effort (or emotional stress which is not mentioned anywhere in the DSQ) that PEM can be triggered.

In summary, if you're going to use the flawed DSQ questionnaire, you'll be limited in studying a specific subgroup of patients that wilts at the most minimal effort and is ineffective at avoiding PEM, which is only a fraction of patients with ME/CFS.

I haven't seen statistics of his many patients are mild, moderate vs. bedbound and severely ill, but I'd guess that the severely ill are fewer in number, with the vast majority of patients being milder, but still quite ill, and insights learned studying these mild to moderate patients could have a far greater overall benefit, in numbers of patients helped, as reducing PEM is a big factor in our difficult climb to wellness.

What's needed is the development of a better tool than the DSQ, one which elucidates when and how PEM is triggered, how much PEM, and under what conditions, and includes emotional, cognitive, and physical effort. In this way, patients might be able to be selected for studies in subgroups, which might result in more comprehensive knowledge about this vexing condition in the long run, helping more of us in the patient population.

Thank you for your effort in this important work.

Sincerely,

[...]

[...]

Dear Sir - I bring to your attention six peer-reviewed published manuscripts attached below, which are now being reviewed by The World Health Organization, The Harvard School of Public Health, and The Lancet Commission on Pollution and Health. The silicone breast implant debacle of the early 1990's is repeating itself, and it has direct relevance to generalized environmental toxicity and the epidemic of fibromyalgia (FM), chronic fatigue syndrome (CFS), and multiple other vague syndromes. Breast implants are just one of 60,000 man-made organosiloxane molecules that contain artificial silicon-carbon bonds (with such bonds never occurring in nature). These 60,000 compounds now contaminate every environmental compartment, causing alarm bells to go off at the above organizations. These molecules are essentially a "mission impossible" for any living

organism to handle, and in that regard you may find the “biophysics” section of “Vague Syndromes” the most interesting. Dysfunction of epigenetic factors, mitochondria, the immune system, the microbiome, the autonomic nervous system, the central nervous system, cytokines, and all basic metabolic processes are inevitable occurrences from exposure to organosiloxanes. Silicon behaves like a metal at times, so the biointegration of organosiloxanes and/or their degradation products (silanols, etc.) into life-sustaining molecules changes their electromagnetic fields. This, in turn, disrupts the communication networking of these molecules. Researchers investigating the varied clinical phenomena (noted above) in CFS are having tunnel vision. Stated more simply, neurologists, infectious disease specialists, immunologists, and rheumatologists have been looking in the wrong place far too long. Silicone breast implant toxicity is a genuinely novel illness caused by over two dozen disruptions of the body’s biochemistry, virtually none of which have anything to do with autoimmunity, but virtually all of which are directly related to CFS. I would recommend googling a recent article by Dr. Cara Tomas and associates at Newcastle University in the UK, published in Plos One on October 24, 2017, entitled “Cellular Bioenergetics is impaired in Patients With Chronic Fatigue Syndrome.” Decades of assertions by physical chemists that organosiloxanes are chemically and biologically inert are now known to be false. Compared to other environmental contaminants (e.g., organophosphates, heavy metals, polyhalogenated molecules, etc.), organosiloxanes are the most disruptive to life on earth as we know it. A simple example of this is the decimation of honeybees caused by organosiloxane surfactants (the insecticides themselves have nothing to do with it). When the electromagnetic fields in the brains of honeybees become dysfunctional, they can no longer hone back to the hive, so they fly around in disarray until they become exhausted and then they die. Do you know any individuals with chronic fatigue syndrome who have disorientation (i.e, they drive into the wrong neighborhood)? Researchers focusing on immune dysfunction in honeybees (and potential viral infections) are also having tunnel vision. The “chronic” in chronic fatigue syndrome is likely due to the perpetuation of the organosiloxane-induced epigenetic dysfunction of histones, micro RNA’s, and DNA methylation from one cell division to the next (and yes, this likely also occurs in the DNA of mitochondria, not to mention the enzyme dysfunction of the electron transfer system). An elegant article on epigenotoxicity was published on June 27, 2016 by Dr. Ibrahim in Advances in Clinical Toxicology. However, the focus on endocrine receptor dysfunction for the past two decades is also likely to be tunnel vision - this is a gross oversimplification, and endocrine dysfunction from chemical toxicity is (in my opinion) an epiphenomenon that, at best, is probably circuitously reinforcing. Lastly, I bring to your attention the Magnesphere, a treatment that may offer some help (a seventh attachment below will explain this). All other allopathic and/or alternative medicine treatments appear to be an exercise in futility for most sufferers of CFS (I have written a book on alternative medicine, but unfortunately help is hit or miss with CFS once the severe chronicity sets in). Please feel free to disseminate this information (and all eight attachments) to anyone else. Sincerely yours, [...]

[...]

January 13, 2018

Dear NINDS,

I am writing regarding NINDS Common Data Elements for ME/CFS.

I’m a bedridden, 34 year ME sufferer, sick since 1983 when I had mono and a severe strep throat at the

same time. I'm writing because I'm concerned about the measure of PEM using Lenny Jason's DePaul Symptom Questionnaire (DSQ). I'm not well enough to write more at this time but I hope reevaluation and rewriting with full consideration of the feedback you are receiving will take place to create a more accurate measure of PEM.

Thank you.

[...]

[...]

Hi –

I hope I can make a comment even though I'm not a citizen in the US. I'm

female. 48 years old. Not in menopause.

WEIGHT GAIN – I Think WEIGHT GAIN IS A MAJOR ISSUE IN ME

I used to be tall and sporty with a weight of 65 kilograms. Now I'm tall and kind of fat with a weight of 85 kilograms. This weight gain has come during the last two years.

Everything I eat converts to weight gain. I don't overeat. I eat healthy food. I think that hormones like leptin and ghrelin could be playing a role.

My TSH is normal – so the doctors here I DK won't measure free T3 and free T4 – or reverse T3 for that matter.

Thank you,

[...]

[...]

I've had cfs since i was 26 years old. I am now 56 years old. This illness along with fibromyalgia has destroyed my life. I was a runner for ten years. five miles a day six days a week. I lifted weights three times per week. I feel like mine came on as a viral illness. I kept going to the doctor to be checked for mono because that is what it felt like but the test was always negative. Two years later i tested positive for Epstein Barr. I have a sister and a half sister with fibromyalgia. Autoimmune illnesses run Int fromin my family. I just want someone to know my story. Yahoo Mail on Android

[...]

Hi,

I'm a patient and would like to comment on the MECFS CDE PEM subgroup document found here: [https://www.commondataelements.ninds.nih.gov/Doc/MECFS/04_Post-Exertional Malaise Subgroup CDE Draft Recommendations.pdf](https://www.commondataelements.ninds.nih.gov/Doc/MECFS/04_Post-Exertional_Malaise_Subgroup_CDE_Draft_Recommendations.pdf)

The document defines PEM as response to minimal amounts of exertion.

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

What minimal means is open to a wide range of interpretations. In my view, the PEM threshold is a function of illness severity and recent activity levels. At the milder end of illness severity, the amount of exertion tolerated by the patient would probably be considered more than minimal by most. There is some risk that if PEM is defined as only occurring in response to minimal exertion that the subgroup of patients with recent and gradual onset will not be studied and diagnosed, when early diagnosis and intervention could be key to improving long term outcomes.

The description of PEM by the National Institute of Medicine that follows the quote above is good. In contrast, the DePaul Symptom Questionnaire, PEM subscale is a poor instrument to accurately assess PEM in my opinion. It doesn't capture the full range of symptoms, and emphasizes tiredness and soreness which are normal responses to physical activity, whereas in PEM the type of symptoms experienced in response to exertion are abnormal (such as markedly decreased sleep quality, malaise as if sick, heart rate that remains elevated for days, lower body temperature, etc). Other important aspects of PEM are also that these symptoms occur with a delay.

Questionnaires to assess whether the patient is suffering from PEM cannot be based on the assumption that the patient is regularly overexerting themselves, because patients will over time learn to reduce their activity levels so that PEM is avoided. I think this may be especially a concern with children because they have fewer responsibilities and more freedom to reduce their activity levels than adults. Long term patients or those using the technique known as heart-rate monitor assisted pacing may be especially good at avoiding overexertion. On the other hand, many patients also report finding it very difficult to avoid overexertion because they feel good during exertion and don't notice that they went above their PEM threshold until the next day. For these reasons, a PEM questionnaire should assess whether the patient is experiencing PEM or alternatively has been forced to change their behaviour to avoid PEM.

One of the goals of research should be to develop a practical and objective test for PEM. There are probably significant autonomic nervous system and metabolic abnormalities that occur during PEM which could serve as basis for a diagnostic test.

Thank you for giving patients the opportunity to provide feedback.

[...]

Name of Reviewer/Institution: [...] CDE, Case

Report Form or Measure: Chalder fatigue

questionnaire (Fatigue) Suggested Change:

Don't use the Chalder fatigue questionnaire

Rationale:

The Chalder Fatigue questionnaire has two separate scoring systems, bimodal (0-11) and Likert (0-33) [1]. Some of the issues raised below are more significant with one system rather than the other.

(i) Doubts about the validity of two of the items in the questionnaire as means to measure fatigue:

The item "Do you have problems starting things" seems as though it could relate more to motivation or some other issue rather than fatigue specifically. The item "Do you feel sleepy or drowsy" relates more to sleepiness than fatigue. Sleepiness and fatigue are not necessarily the same thing [2].

Most studies that used the Chalder fatigue scale do not give details of scores on individual items but one study [3] reported the following in participants with ME: "Focusing on the individual items revealed that 86.8% of the questions making up the physical fatigue subscale received near maximal or maximum scores. The items which received the greatest number of low scores were question 3 ('do you feel sleepy or drowsy') and question 4 ('do you have problems starting things')."

(ii) Ceiling effects are a significant issue when the Chalder fatigue questionnaire is used with patients with ME and CFS score, particularly with bimodal scoring:

A study of those with ME [3] found that "Fifty per cent of the patients recorded the maximum score using the bimodal method and 77% recorded the two highest scores [i.e. either 10 or 11]." In the FINE and PACE trials, 76% (147/193) and 65% (417/640) respectively of CFS participants reported the highest score [11] at baseline using bimodal scoring [4,5].

With regards to Likert scoring, a study of those with ME found that there was some evidence of a ceiling effect in those who were severely affected (more details were not reported but the average score for those severely affected was 30.55 (SD: 2.66)). In the FINE and PACE trials 29.1% (57/196) and 14.5% (93/640) of the participants with CFS respectively scored the maximum score of 33 at baseline.

There is also a 14-item version of the instrument with three extra items. A study of 136 individuals with CFS looking at Likert scoring found there was near- maximal scoring on 6 of the 8 physical fatigue items [6].

The authors of the ME study [3] noted with regards to bimodal scoring that there was a "marked overlap between those who rated themselves as moderately or severely ill. These findings are indications of a low ceiling." This could lead to the questionnaire failing to detect patients moving from being severely to moderately affected and vice versa.

Furthermore, if patients are already at a ceiling score at the start of the intervention, the questionnaire cannot detect their getting worse. This could mean that evidence of harm would not be recorded. Also, this phenomenon could affect measures of efficacy: if a certain percentage of patients improved and the same percentage worsened to a similar level, this could show up as an average improvement because the scores for those who got worse would not change if they were already at the ceiling level.

This could also make interventions that caused a significant number of deteriorations seem better than those that caused fewer. For example, consider a scenario in which one intervention caused a certain percentage of patients to improve while the same percentage, who began at the maximum score, worsened by the same amount. If another intervention caused half the number of patients to both improve and worsen, the average numerical improvement for the first intervention would be twice that of the second, even though rationally the scores should be the same.

(iii) Discussion of the ability of respondents to mark symptoms as occurring "less than usual":

The fact that participants can rate their fatigue symptoms as occurring "less than usual" can lead to some odd results with Likert scoring of the Chalder scale (it is not an issue with its bimodal scoring). People who have no fatigue problems should generally score 11/33, indicating that they had problems 'no more than usual'. And, indeed, a study in Norway found that those in the category "No disease/current health problem" had a mean score of 11.2 [7].

However, a study found that people with "multiple sclerosis fatigue" after an intervention reported an average fatigue score of 7.80 - that is, lower than 11; this score also showed lower fatigue than that of a healthy, nonfatigued comparison group in the study [8]. It is very unlikely to be true that patients with multiple sclerosis fatigue at baseline ended the study with lower fatigue than healthy people. Scores of less than 11 were also reported by those with CFS in the FINE and PACE trial [4,5].

I will explore further now how pooling the scores of people who give scores of less than 11 with other scores can give odd results. Say 75% of participants gave a Likert score of 4 and 25% gave a score of 24. This would be an average score of 9 which is a better score than the score of 11 that healthy people report. However, it is likely that people who scored 4 on the scale were confused by the peculiar option on the Chalder questionnaire that allows them to rate themselves as having fewer problems with fatigue than when they were last well (choosing that option is the only way to get a score below 11). If they really meant to say that they had no more fatigue than when they were last well, then their score should really have been similar to that of the average healthy person, at 11.2. Substituting this score instead of 4 in this example would give an average score for the group of 14.4, a worse score than what healthy people score. The latter is, I believe, a better representation of what the average fatigue score for the group would be: that is, if a significant percentage still had significant fatigue, then the overall fatigue level should be worse on average than a healthy group, not better. This shows that the ability to have better scores than healthy people doesn't just affect the validity of individual scores, it also affects the validity of overall mean scores.

References:

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[...]

Dear Sir,

I send you the comments
regarding the ME / CFS Document

[...]

[...]

To: NINDS/CDC Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

GENERAL COMMENT OF THE CFS DOCUMENT

Dear gentlemen,

First of all, thank you, from the [...], for the opportunity to review this document.

I send you my comments, based on clinical experience, for about 10 years, that we have an [...], which currently controls about 2300 CFS cases, according to the criteria of Fukuda and Carruthers 2003, we have verified that 100% of them would meet criteria of IOS 2015 and 90% of Carruthers 2011.

I think the document is very well structured.

Regarding the work subgroups, I would be a specific one of the comorbid phenomena associated with the CFS, which have a specific weight in the integral assessment of the CFS patient.

And I also think it would be important to work on the chronic fatigue associated differentially with the following entities:

- Cancer survivor: We control about 130 cases, the clinical characteristics are very similar and it is one of the most differentiating problems in modern oncology, in this respect the American Oncology Guidelines of 2017 reflect this and I think it would be important to establish consensus groups at international level and that the primary CFS group could provide sufficient experience in the constituted working groups.

-Chronic fatigue in immunoinflammatory diseases. We control about 170 cases, affected by entities such

as inflammatory bowel disease, multiple sclerosis and disseminated lupus erythematosus. These patients in my opinion would represent a specific subgroup, with little clinical expression of the target organ

and in which fatigue, would condition a severe limitation, predominantly determined by the cognitive dysfunction associated with said process . And I believe that, just as in the fatigue of the cancer survivor, groups of international consensus should be established, for the optimal management of these patients, not focusing only on psychological aspects.

- Chronic fatigue in chronic intracellular infections (hepatitis C, B, HIV, polio, Borrelia, etc.). We controlled about 150 cases, where also chronic fatigue, would establish a differential subgroup, without liver biological injury in hepatitis viruses, without opportunistic infections in HIV infection, with scarce neurological clinical expression in the infection by the virus of the polio and the clinical expression of possible chronic Lyme in the case of Borrelia infection. Recently, it has been proven that after the eradication of the hepatitis C virus, the central fatigue does not change. I believe that these models of chronic fatigue in intracellular infection can serve as a model in basic research for example. In this same point, highlight the impact that fatigue, represents in the survivor to the infection by the dengue virus and ebola.

GROUP COMMENT

Baseline

-Important consensus, everything that has to be evaluated in the clinical history, physical exploration and complementary explorations (laboratory, image scans), among others and use all the same model, to start an international online registration, as soon as possible .

- With these results we can have a correct phenotyping of the patient affected by CFS, with the help of the methodology that systems biology can provide.

Fatigue

- Prepare a questionnaire of specific questions regarding fatigue.

-Use the questions about fatigue, which Jason's questionnaire establishes.

- Good experience with the modified fatigue impact questionnaire, with the global score score, the physical, cognitive and psychosocial subscale.

- A scale of quantification of fatigue should be agreed by the international group and used by all the scientific community.

Intolerance to physical exercise

- Consider in the assessment of the patient the block of muscular symptoms, as reflected in the diagnostic criteria of Carruthers.

- It is important to take into account the questions about this symptom in the Jason questionnaire.

-Consensus the ergometric test that will be performed, to assess the physical functional capacity of the patient with CFS. It seems to me of interest, to perform the test of the two consecutive days in the basal or initial assessment and then ergometric test before and after any therapeutic intervention or for basic and clinical research purposes.

-It is important that the professional who performs the test and the corresponding report, has a proven experience with the patient affected by CFS.

- Establishing this subgroup well in my opinion is necessary, since I consider the CFS, as a process with severe intolerance to physical exercise, which conditions a severe functional limitation, both in

labor activities as personal and / or social.

- Consensus should be established on the degrees of intolerance to physical exercise, which are indicative for the individualized therapies of programmed physical exercise and also the assessment of the corporal damage of these patients.

- Studies should be carried out that assess the association between intolerance to physical exercise with cognitive and neurovegetative symptoms. And practice brain and muscle neuroimaging and biological parameters (genomics, proteomics and metabolomics), before and after performing physical exercise.

Sleep dysfunction

- It is important to take into account the questions about this symptom in the Jason questionnaire.

-Study through the symptomatology, the characteristics of the dream: non-restorative sleep, insomnia, daytime hypersomnia, drowsiness, with the corresponding questionnaires that must be agreed by the different groups.

- Good experience with the Pittsburg sleep quality questionnaire.

-Exhaustive study of the comorbid phenomena of sleep, through the use of questionnaires and polysomnographic study of sleep, such as restless legs syndrome and sleep apnea syndrome among others.

-It is important to consider this subgroup, given the impact of the symptomatology, given that in my opinion in CFS, it is a medical process that induces non-restorative sleep.

-To promote the basic investigation of sleep dysfunction, with different electrophysiological techniques, neuroimaging and biological parameters.

Pain

- Prepare a questionnaire of specific questions regarding pain.

-Use the questions about pain, Jason's questionnaire establishes.

- Use the analog pain scale and the brief pain questionnaire.

- The McGill questionnaire, may be interesting to assess pain, in our experience offers a difficulty in answering it adequately by many of the patients.
- In the assessment of pain in patients affected by CFS, it is important to assess, diagnose and correctly treat comorbid pain-inducing phenomena such as fibromyalgia, vertebral degenerative arthropathy, tendinopathies, patellar chondropathy, carpal tunnel syndrome and plantar fasciitis. among others.

Neurocognitive

- Consider in the assessment of the patient the block of neurocognitive symptoms, as reflected in the diagnostic criteria of Carruthers.
- It is important to take into account the questions about this symptom in the Jason questionnaire.
- Good experience with the Waiss 4 and (Santamarina P, 2014), for detection of neurocognitive dysfunction, through neuropsychological scales.
- To agree on the objective tests for assessment of neurocognitive dysfunction, neuroimaging and biological parameters.
- To agree on the objective tests for assessment of neurocognitive dysfunction, neuroimaging and biological parameters.
- The information collected in this block, as in the rest, must be homogeneous and it must be agreed, which parameters of neurocognitive vegetative dysfunction, are included in the patient's study.
- Establishing this subgroup well in my opinion is necessary, since I consider the CFS, as a process with severe neurocognitive dysfunction, which conditions a severe functional limitation, both in labor activities as personal and / or social.
- They must perform biological and neuroimaging studies, which assess the association with neurovegetative symptoms and intolerance to physical exercise, both at baseline, as well as after physical, intellectual stimulation, in a lying or in orthostatism situation.

Neurovegetative

- Consider in the assessment of the patient the block of neurovegetative symptoms, as reflected in the diagnostic criteria of Carruthers.
- It is important to take into account the questions about this symptom in the Jason questionnaire.
- Good experience with the Compass 31 questionnaire, of neurovegetative dysfunction.
- To agree on the objective tests for assessment of neurovegetative dysfunction, such as intestinal, bladder, and tilt table studies, for example.
- Excellent experience, with the determination of R-R variability, using bloodless methods, through the use of new mobile devices.
- The information collected in this block, as in the rest, must be homogeneous and it must be agreed, which parameters of neurovegetative dysfunction, are included in the patient's study.
- Establishing this subgroup well in my opinion is necessary, since I consider the CFS, as a process with severe dysfunction of the neurovegetative system and must perform biological and neuroimaging studies, which assess the association with cognitive symptoms and intolerance to physical exercise , both at baseline, as well as after physical and / or intellectual stimulation.

Neuroendocrine

- Consider in the assessment of the patient the block of neuroendocrine symptoms, as reflected in the diagnostic criteria of Carruthers.
- It is important to take into account the questions about this symptom in the Jason questionnaire.
- To agree on the objective tests for assessment of neuroendocrine dysfunction, neuroimaging and biological parameters.
- The information collected in this block, as in the rest, must be homogeneous and it must be agreed, which parameters of neuroendocrine dysfunction, are included in the patient's study.

-They must perform biological and neuroimaging studies, which assess the association with neuroendocrine symptoms and intolerance to physical exercise, cognitive dysfunction, neurovegetative dysfunction, both at baseline, as well as after physical, intellectual stimulation, in a lying or in orthostatism situation.

Inmune

- Consider in the evaluation of the patient the block of immunoinflammatory symptoms, as it is reflected in the diagnostic criteria of Carruthers.

- It is important to take into account the questions about this symptom in the Jason questionnaire.

-The information collected in this block, as in the rest, must be homogeneous and it must be agreed that immunological analytical parameters are included in the patient's study.

- Establishing this subgroup well is my basic opinion, since I consider the CFS, with a medical process with an immunoinflammatory base.

Quality of life and CPET

- Prepare a questionnaire of specific questions regarding of quality of life.

- Good experience with quality-of-life and functionality questionnaires SF-36, Euroqol-5 and Karnofsky performance scales.

-Consensus the ergometric test that will be performed, to assess the physical functional capacity of the patient with CFS. It seems to me of interest, to perform the test of the two consecutive days in the basal or initial assessment and then ergometric test before and after any therapeutic intervention or for basic and clinical research purposes.

Biomarkers

-I consider it of great interest, in basic research with subsequent application in the clinic, within the context of translational research, with the aim of obtaining biomarkers, not only diagnoses, but also for future therapeutic targets, which can modify the chronic course of the process.

-The research in genoproteomics, metabolomics, immune response and oxidative and

mitochondrial metabolism, among others, should be prioritized. And always with broad samples of cases very well phenotyped clinically and that includes samples from different countries.

-Also, I consider it important to prioritize research projects with longitudinal design, which would allow us to better understand the clinical course of the CFS.

[...]

Thank you for asking the [...] to contribute to the discussion on CDEs.

Several researchers and senior academics met to discuss the CDEs. The attached document has been agreed by all present. We hope it will be useful.

Yours

[...]

Feedback about CDEs

[...]

We were delighted to be asked to comment on the common data elements. We agree that having a unified set of data that should be collected across studies is needed to enable comparison between studies and analyses across data sets.

Major concerns:

1. Our major concern was the size of the questionnaires and the lack of clarity about which questions were “core” or essential and which were desirable. In our experience, patients with CFS/ME take longer to complete questionnaires because of their cognitive symptoms and fatigue. Questionnaires that will take 20 minutes in a healthy person, can take hours in a patient with CFS/ME.

RECOMMENDATION: The Common Data Elements should be reviewed and reduced to reduce patient burden. Questions could be categorised as core/essential or desirable.

2. Our second concern was about whether there has been sufficient patient involvement. It wasn't clear how many of the questionnaires used have been tested in patients with CFS/ME and whether there is face validity.

RECOMMENDATION: Patients need to test the proposed questionnaires to check the feasibility of completing such an exhaustive list, the length of time it takes and whether questionnaires capture the data as expected (or whether there are particular problems with questionnaires or individual items).

3. It is not clear who is expected to complete the questionnaires: physician, patient or carer.

RECOMMENDATION: It needs to be clear who is expected to complete the CDEs

Other concerns:

1. **Baseline/Covariate Information:**
 - Several of the questions/answers are not relevant for those outside the USA. For example: race, marital status, benefits. These will need to be adapted if used outside the USA.

- The questionnaire is very large and will pose an excessive burden on patients. Not all the questions are “core”, (e.g a page on nasal symptoms).
 - Question 69 needs ‘other’ box to be available
- 2. Fatigue:**
 - It wasn’t clear if the Krupp scale was appropriate for this patient group. It has not been used routinely in previous epidemiological studies in CFS/ME.
 - 3. Post-Exertional Malaise:**
 - We would recommend that this is tested with patients to check that PEM can be identified or whether further questions are needed.
 - We do not believe that patients will be able to remember episodes of PEM 6 months ago. Normal recommendations for time periods on questionnaires is 2 weeks. We recommend the groups ask patients to review the questions and potentially seek advice from those involved in the methodology of developing patient reported outcome measures.
 - 4. Pain:**
 - We were not convinced there was sufficient data collected on the different types/location of pain.
 - It may be that a recommendation on some of the smart phone mapping methods for pain might be helpful as a method of reducing patient burden and increasing the detail of information about pain collected. Types of pain need defining more precisely.
 - In some cases more objective methods to collect data about pain would be helpful E.g. Qualitative Sensory Testing
 - 5. CNS:**
 - We remain concerned about patient burden and recommend a maximum length of time that patients undergo investigations.
 - 6. Immune:**
 - The group was very concerned about this section which appeared to ask questions that were rarely going to be relevant and were at times considered impossible to answer. E.g. “how close are you to a vehicle idling area?”
 - We recommend that questions and tests are divided into essential/core and additional/desirable. At the moment, it appears that all possible tests have been included which will allow investigators to continue to use different tests therefore undermining the principals of the Core Data Element.
 - 7. Quality of Life:**
 - Testing with patients suggest the WHODAS is the preferred method to collect data on QOL
 - 8. Biomarkers:**
 - The recommendations are somewhat “dated” and could be updated to reflect current technological advancements (for example, including the translactome)
 - We are concerned that insufficient information is collected on sample handling and pre-treatment and recommended review by a laboratory manager. Please see [...]

Other points:

- We feel it is important that mood disorders are measured carefully to enable patients with primary mood disorders to be excluded and also to help interpret results in those with co-morbid mood disorders. We did not identify a screening questionnaire for mood disorders.
- We believe there is repetition in questions between different groups. For example, sleep questions are asked in more than one section.

[...]

I am an ME patient. I tried to fill in online form but it would not allow me to submit. I strongly disagree with the proposal to use a section of the De Paul Questionnaire, to assess or ask about PEM. This questionnaire is far too loose and will not ensure the selection of ME/CFS patients only. Patients with fibromyalgia or depression could also give positive responses to questions posed. The de Paul Questionnaire is not fit for purpose. The description of PEM based on the IOM report describe my experience of PEM far better. I would be happy for this to be used.

It is so important to recognise that PEM occurs after mental or cognitive exertion. I can meet a friend for coffee for 45 minutes. If I stay longer I will get PEM. This means I must lay in a quiet room. PEM will result in pounding heart, arrhythmia, burning skin, tinnitus, inflamed feeling in my head, air hunger and a general poisoned feeling. I will have to remain a minimum of 2 to 3 hours in complete rest for symptoms to ease. I will feel wiped for the remainder of the day, completely exhausted. My head will feel fuzzy the next day, I will still not be back to my baseline. Phone calls, concentrating on writing emails can trigger a milder PEM which would not be as severe. I get PEM from physical exertion but it is easier avoid it by staying at rest and housebound most of the time.

Please do NOT use the de Paul Questionnaire, it is not fit for purpose. Please get this right, ME patients are suffering for so long, please get it right, lives and dreams are at stake.

Thank you.

[...]

Please find below our submission on problems with the Chalder Fatigue Questionnaire. As requested, we have detailed our submission in the body of this email, however we have also attached a PDF version for ease of readability.

On behalf of the working group, thank you for providing the opportunity for patients to provide feedback, we hope that this level of collaboration continues as it is greatly appreciated.

Regards

[...]

Submission to the public review on common data elements for ME/CFS: Problems with the Chalder Fatigue Questionnaire

[...]

The Chalder Fatigue Questionnaire (CFQ; Chalder et al., 1993) is among the scales being proposed to provide common data elements (CDEs) on fatigue for future NIH- and CDC-funded studies of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Because the CFQ was used in the PACE trial it has received close scrutiny from patients and researchers who have been critical of the trial (e.g., Wilshire et al., 2016). Some of those same individuals were involved in the drafting of the present submission.

The Chalder Fatigue Scale

Many of the problems with the scale are obvious upon inspection, and so it is important to examine the scale. The complete scale, in its final 11-item form, is reproduced below (bolding is ours).

*We would like to know more about any problems you have had with feeling tired, weak or lacking in energy in the last month. Please answer ALL the questions by ticking the answer which applies to you most closely. If you have been feeling tired for a long while, then compare yourself to how you felt **when you were last well**.*

1. Do you have problems with tiredness?
2. Do you need to rest more?
3. Do you feel sleepy or drowsy?
4. Do you have problems starting things?
5. Do you lack energy?
6. Do you have less strength in your muscles?
7. Do you feel weak?
8. Do you have difficulties concentrating?
9. Do you make slips of the tongue when speaking?
10. Do you find it more difficult to find the right word?
11. How is your memory?

The scale items can be scored 'bimodally' or with 'Likert' scoring, as shown below. The scores for each item are then summed to produce an overall score.

Response	Bimodal score	'Likert' score
Less than usual	0	0
No more than usual	0	1
More than usual	1	2
Much more than usual	1	3

Problems with the scale

1. Few items appear clearly related to fatigue

Only three of the eleven items on the scale (#1, #2 and #5) appear to be clearly related to fatigue. For the rest, the scale assumes that memory problems, speech errors, sleepiness/drowsiness, muscle weakness and so on are indicators of fatigue, and that the more such symptoms a patient reports, the greater their overall fatigue. These assumptions are untested and their basis is unclear.

The item on 'problems starting things' is particularly puzzling. It appears to be probing for lassitude, a common symptom in depression. Indeed, similar items appear in several depression scales, such the Montgomery-Asberg Depression Scale (Montgomery & Asberg, 1979). The relationship of lassitude to fatigue outside the context of depression is unknown.

Chalder et al. (1993) defined 'caseness' as a bimodal score of 4 or more on the CFQ, which means that a patient could be defined as a fatigue case if their only symptoms were difficulties in concentrating, making slips of the tongue, word-finding, and having memory problems. This appears to be entirely inappropriate, since it is unclear whether any of these symptoms are effective at discriminating between those with fatigue and other types of complaints (for example, mild cognitive impairment).

The lack of obvious or validated relevance to fatigue of the majority of items on the scale would, on its own, appear to make the CFQ unfit for purpose as a fatigue scale.

2. Focus on change in fatigue rather than intensity

The CFQ asks patients who have been feeling tired for a long while to rate their fatigue compared to when they were last well. It does not take 'no fatigue' as its baseline.

For ME/CFS patients – who, by definition, must have been ill for some time in order to achieve a diagnosis – this means remembering how it felt to be well. Patients may have been unwell for anything from several months to several decades and their recollection may well not be accurate.

An added source of confusion is that respondents are told to compare themselves to 'when [they] were last well', but the response options ask whether respondents are having problems 'less/more than usual'. 'Usual' to a patient with a chronic illness such as ME/CFS is clearly not the same as 'when [they] were last well', and this conflicting wording is likely to lead to response errors.

The fact that respondents can mark each fatigue problem as occurring 'less than usual' is also problematic. It is unclear how anyone could feel less tired than when they were well, and therefore unclear what a respondent means when they select this option. Confusingly, a score of zero on the 'Likert' scoring of the CFQ is therefore not the base-point of the scale; a patient who scores 11/33 is no more fatigued than when they were last well, not one who scores 0/33. This makes interpretation of the scale difficult.

3. Arbitrary weighting of physical and mental components

Chalder et al. (1993) report a principal components analysis indicating that the scale has two major components – mental and physical fatigue. They combine these into a single score in the CFQ but the weighting of these components appears arbitrary, and is based simply on the number of questions of the two types in the questionnaire.

Even putting aside concerns about the validity (particularly of some of the 'mental' fatigue items), the consequence of combining mental and physical fatigue questions is that the scale is not necessarily monotonic, as an improvement in one form of fatigue could be accompanied by a worsening of the other type.

4. Incompatibility of scoring schemes

There are two alternative scoring methods. The 'bimodal' method assigns a 0 or 1 to each response, depending upon whether the complaint is present or absent (maximum score 11). The 'Likert' method rates each response from 0–3. The minimum score of 0 is given only for 'less than usual' (paradoxically *less* fatigue than before illness). A response of 'no more than usual' scores a higher 1, even though it indicates full recovery. Scores of 2 and 3 are given for 'more than' and 'much more than' respectively (maximum score 33).

The relationship between the two scoring schemes is far from transparent. One of them counts the number of symptoms, the other weights the intensity of the symptoms (and confusingly, gives extra credit for being *even better* than before the illness). Indeed, these two methods can generate contradictory findings: in the PACE trial, in 23 cases, fatigue scores decreased during the course of the trial based on one scoring method, but actually increased based on the other method.

Dataset available at https://sites.google.com/site/pacefoir/pace-ipd_foia-qmul-2014-f73.xlsx?attredirects=0, 'readme' file <https://sites.google.com/site/pacefoir/pace-ipd-readme.txt?attredirects=0>

5. Failure to directly measure fatigue intensity

In the table on p.3 of the Fatigue Subgroup Materials section of the CDE Public Review document (NINDS/CDC, 2017), the CFQ is described as an index of 'fatigue intensity'. As noted above, the bimodal scoring method simply yields a count of symptoms on a present/absent basis, while the 'Likert' version blends the number of symptoms with their intensity in a manner that is impossible to interpret from the total score.

6. Ceiling effect

Kindlon (2010) has pointed out that findings reported by Morriss et al. (1998) indicate that ceiling effects are likely when the CFQ is used. These investigators applied the questionnaire to 136 CFS patients in an outpatient clinic, and reported near-maximal scoring on six physical fatigue-scale items from the questionnaire, irrespective of which scoring method is used.

Clearly, it is important to know whether ME/CFS patients are experiencing worsening fatigue – or even harm – in response to an intervention. It is also important to know whether fatigue correlates with a potential biomarker. The CFQ's ceiling effect is therefore a problem.

Conclusions

We have here identified a number of serious problems with the CFQ, and note that the Fatigue Subgroup Draft Recommendations document also summarises some problems with it (p.33, our bolding):

Scoring:

'This instrument can be scored in two ways: Bimodal and Likert scoring. It appears that the choice of scoring method may result in significant differences in interpretation of outcomes. (Rebecca Goldin. Sense About Science USA. March 21, 2016 <http://www.senseaboutscienceusa.org/pace-research-sparked-patientrebellion-challenged-medicine/>). **This will need to be further researched.**'

'Thresholds have been reported for both methods. (Bimodal: Case (≥ 4) vs. non-case (< 4) Mean

score = 9.14 (SD 2.73) and 3.27 (SD 3.21) for Community sample. Mean “Likert” score 24.4 (SD 5.8) and 14.2 (SD 4.6)). However, the study referenced for these thresholds in the Chalder instrument required patients to meet either Oxford or Fukuda. As NIH’s ME/CFS Pathways to Prevention report noted, Oxford could have selected patients with other fatiguing conditions. Thus, it is difficult to know if these thresholds apply to ME/CFS cohorts. **Further research is needed.**’ (*typo is first line of quote was corrected by us*)

We are pleased to see these problems acknowledged, but concerned to see a call for further research on a questionnaire which appears unfit for purpose, and which is unlikely to become so with even major modification.

We would much prefer to see a questionnaire developed from the ground up: one that begins with researchers conducting a narrative interview, and then identifies items worth including on the basis of their ability to discriminate severely fatigued individuals from healthy ones. Perhaps one already exists and is being considered – we do not know the wider literature – but it is clearly not the CFQ.

We are pleased also to see (p.6 of the document) that the Fatigue Subgroup is aware that a challenge in assessing fatigue in ME/CFS is not only symptom variability, but also that symptoms are exertion-dependent. It is perfectly possible for a patient who is very severely disabled by ME/CFS to experience little fatigue most of the time because they are pacing themselves and restricting their activities to remain below their fatigue-triggering threshold.

We are grateful for the opportunity to contribute to the development of common data elements for our disease and will follow the work on this with great interest.

[...]

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NINDS/CDC. Public Review Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Common Data Elements (CDE) Fatigue Subgroup Materials. 2017. Available at: https://www.commondataelements.ninds.nih.gov/Doc/MECF5/03_Fatigue_Subgroup_CDE_Draft_Recommendations.pdf

Wilshire C, Kindlon T, Matthees A & McGrath S. Can patients with chronic fatigue syndrome really recover after graded exercise or cognitive behavioural therapy? A critical commentary and preliminary

[...]

Hi,

I'm a patient and would like to comment on ME/CFS CDEs, specifically the neuroendocrine subgroup draft located here:

https://www.commondataelements.ninds.nih.gov/Doc/MECF5/09_Neuroendocrine_Subgroup_CDE_Draft_Recommendations.pdf

Based on discussions with other patients, there may be a potentially important abnormality that's common in ME/CFS, yet rarely mentioned in the literature, and which involves a subtle problem with blood sugar regulation. These patients report episodes of unexplained and objectively measured episodes hypoglycemia in absence of an identifiable endocrine disease. Glucose tolerance tests lasting 5 hours may be suitable to detect this problem. Many patients also report feeling better with frequent small meals which could be due subtle problems in blood sugar regulation. I therefore suggest adding a question that could highlight problems of this type to the symptom questionnaire, as well as investigating this aspect in future studies.

Thank you

[...]

Please find attached my comments for the baseline/covariate form. Will try to comment on other forms and will come back to you in due course.

My general view is that it is quite good and comprehensive, but too long, but I am sure the idea is to start with such questionnaires and then decide on the minimum data that is required, which will be a fraction of what we have now.

Thanks

Best regards

[...]

Subgroup	CDE, Case Report Form or Measure	Suggested Change	Rationale
core	ethnicity and race	to review the options offered for answers	The current options are appropriate to the United States population, but not for international use.
	demographic	questions for US residents only, suggest making it for anyone internationally	same as above, not clear why US residents only,

	employment question 9	give option other	to make it applicable internationally
	question 12	college/university	as above
	health history	have an alternative simplified version for patients' use (when not completed by doctor)	The number of questions may be excessive and some may not be relevant, remember burden to fatigued patients
	family history	shortened questionnaire for patient's use	as above, appropriate language and length
	family history	ask family history of ME/CFS	useful for family/genetic studies
	question 69	give option 3 months cut-off and have an open space for time since developing symptoms	I think we should be looking for cases with less than 6 months in research and clinical practice - and open space will give specific disease duration, rather than categories only
	question 72a	options for longer periods, such as more than 12, 24, 48 hours	to be in line with commonly used definitions of post-exertional symptoms, referring to 24 hours
	question 74	include more options in between yes and no - like yes more than half of the time, yes less than half of the time	many questions are difficult to answer based on yes/no, as people may experience the problem on occasions only, or frequently, but not always
	question 77	add option between 1 day and less than 1 week	option between 1 and 7 days missing
	question 80	add environmental exposure	often reported in relation to me/cfs, eg chemicals, radiation etc
	question 81-3	ask specifically if diagnosis of me/cfs or similar given by health professional, and which health professional, if a GP, specialist, ME/CFS doctor, alternative therapist, nurse or	gives better information about duration and reliability of diagnosis

		other health professional	
	Q 84	separate medications for fatigue from medications taken for other reasons	enable analysis of data for medications taken for fatigue symptoms or me/cfs
	Q84	suggest asking about medications in the last 3 months and now	patients may have taken medications recently enough to make them ineligible for some studies, although they may not be taking now (they may have stopped 1 or 2 days ago)
	Q86	this can be part of questions on previous illness	to avoid repetition
	CDC questionnaire	give more options for duration of symptoms, including from 3-months, and months with symptom, if less than one year - comments above apply to this questionnaire as well toinnaire - suggest if only this is used, that the questions on symptoms are expanded to cover questions as first/ De Paul questionnaire	reasons as for previous questionnaire
	Physical Examination section 1	allow for repeated entries BP and pulse/heart rate, include whether pulse is regular or not	good practice to repeat rest BP and standing BP should ideally be measured up to 10 minutes to pick up late drops
	PE section 1	include option for metric units	universaly metric is more widely used than imperial, both are useful
	PE pharinx (8)	omit large, use tongue only	there are other tongue abnormalities apart from large tongue
	PE 11	is carotid already part of neck examination? Omit from neck examination.	avoid duplication
	reflexes	be more specific = absent, hypo and hyper	

		or could use + categories from 0 to 4+	
	muscle power	can be more specific, eg MRC scale and specify muscles tested	
	lab test results haematology	add haemoglobin and eosinophils	anaemia is important indicator in me/cfs, eosinophils usually reported together and may be relevant
	lab results - chemistry	add Na, K, Ca (adjusted) Po4, ferritin, B12, CK, bilirubin, folate and vitamin D, am cortisol could be included as well	usually part of initial work-out for ME/CFS and differentail with clinical application
	lab results - urine	add signs of infection and blood in urine	for completion
	Medication and other treatments	add option for reason using medication and separate previous 3 months and now, with entry for why stopped	for completion

[...]

Dear NINDS,

I write as an ME/CFS patient who has experienced PEM at various levels of severity of the disease for some 20 years.

I propose an expanded test for PEM. PEM, does not arrive at a regular frequency as suggested in the DSQ - it is contingent on activity. Patients who pace successfully may report minimum PEM because they sacrifice much activity but this loss of function is not recorded in various scales. Symptoms may also begin more than 24 hours after activity.

The term 'fatigue' should be avoided as it minimises PEM and confounds PEM with the fatigue generally experienced by non-ME/CFS people.

Recommendation 1. A scale should indicate the level of activity a patient can do without incurring PEM and at the same time, the level of activity they sacrifice to remain PEM-free. Adapt and add to the SF-36 scale of physical function to take account of PEM. For each activity, ASK:

Can you do each activity every day without getting symptoms which make you feel worse afterward? (If a respondent answers 'Yes' for every day without symptom aggravation, they don't get PEM.) The range of answers is Yes, every day without feeling worse, I can do the activity sometimes but it takes several hours, several days, several weeks or longer than several weeks to recover, or, I can't do the activity at all.

The activities are listed as in the SF-36 scale, Eg Pushing a vacuum cleaner, **Lifting or carrying groceries**, etc. ADD more minor activities to the list in SF-36 scale eg, cooking, reading, writing sitting up, having a shower, walking within the house, taking a short trip eg shopping, taking a longer trip eg to another city. For my example of the questionnaire table see: [...]

This test can economically produce an index of functionality and PEM-related disability for each level of triggers. It also indicates total severity of ME/CFS.

The SF-36 scale can be further adapted with a more refined list of activities added to allow for the more severely affected. Sensory overload, in the form of sound, chaotic sound as in social activities, vision, smells, consuming the wrong food or drug, vibrations, emotional experience and stress also cause PEM with similar symptoms and should be included. MCS and allergies also combine to cause PEM symptoms.

Many patients, especially those who have not yet been diagnosed and are not aware of the peculiarities of PEM, such as delayed onset, may not be aware that increased activity/exercise is causing their symptoms. They may only be able to articulate feelings of 'fatigue' and getting a cold or flu-like state, which seem to occur at random. They would need a clinical interview by informed medical professional to diagnose their state.

Recommendation 2. Symptoms experienced in PEM should be listed, with degree of symptoms triggered by PEM in order to show the extraordinary nature of PEM, giving scientists an idea of the types of symptom and severity triggered by exertion. It may allow sub-typing of symptoms occurring after activity. ASK: Which of these symptoms do you experience after activity, and what is their impact? For each symptom, state the extent of change that occurs following activity/exertion: None, A bit worse than usual, A lot worse than usual.

Symptoms: heaviness, weakness, sleepy feeling, tiredness, loss of co-ordination, difficulty thinking/concentrating, making simple mistakes, tingling or pricking in some body parts, muscle twitching, muscle pain, joints feel weak/loose/painful, sore throat, flu-like symptoms, sweating, headache, nausea, difficulty standing, dizziness, tinnitus, shakiness, breathlessness, difficulty breathing, difficulty getting to sleep, sleep quality, irregular heartbeat, etc.

Does your heart-rate increase or decrease after increased activity? Does this change last longer than usual? How long does it last?

A composite index of the functionality and symptom worsening test can be constructed to show PEM severity and probably general severity of ME/CFS. Further questions:

- Do your symptoms start during activity, immediately after activity, or are they delayed? If delayed when do the symptoms start? Which is the worst day? (How a patient feels on the day of a test has been shown to make a difference to laboratory test results in some studies.)
 - When you recover from PEM, do you return to your previous level of ability?
 - How long have you had these symptoms worsening after activity/ exercise?
 - Have your symptoms after activity got better, worse or stayed much the same over time?
- The symptoms should be correlated with activity level allowed by PEM in Recommendation 1. above and length, severity and progress of illness.

Thank you for your attention. [...]

[...]

Dear NINDS Working Group,

Common Data Elements (CDE) Baseline/Covariate Information Subgroup Materials

Feedback

I write as an ME/CFS patient who has experienced PEM at various levels of severity of the disease for some 20 years. I would like to make two comments:

1. In the section 'Past and Current Illnesses' it may be useful to add chronically infected tonsils. In Types of surgery it may be useful to add tonsillectomy. Would tonsil conditions be likely to reflect on the functioning of the immune system? I mention this because in the opinion of some doctors this is thought to be the case, especially where chronic infection is involved. Patients can easily forget to nominate this in the List of Other Surgeries, especially if the issue occurred many years prior to ME/CFS.
2. While the CDC Symptom Checklist – Form A does a good job of listing and exploring symptoms, it misses the point that many of the symptoms are triggered or made worse by activity/exercise, rather than occurring as a function of time. It would be impossible for a seasoned patient like myself to answer these questions accurately. The results therefore would not reflect the reality of symptom occurrence. While symptoms may have their own rhythms these rhythms are often obscured, or the symptoms may be triggered mainly by activity/exercise. The DSQ has a similar problem, although it incorporates effects of activity in a separate question.

For accuracy, it would therefore be essential to add an option to the questionnaire to reflect the effect of increased activity. Post-exertional malaise is not a discrete symptom on its own. It is made up of the appearance or worsening of a large number of symptoms which do not normally follow increased activity/exercise.

A more revealing analysis of each symptom might be done as follows: During the past month, how often have you had a sore throat? q 1 A little of the time q 2 Some of the time q 3 A good bit of the time q 4 Most of the time q 5 All of the time, (as current).

Then ASK, Does your sore throat occur without any apparent reason? Yes, No. Does it occur following increased activity/ exercise? Yes, No

State the extent of change in your sore throat that occurs following activity/exertion: None, A bit worse than usual, A lot worse than usual.'

3. Some further acknowledgement of the fact that the illness can last for many years or be life-long and that it can severely limit activity, is needed. Some patients never recover from what seems to be an episode of PEM. The seriousness of symptom impact is truncated in this questionnaire. Eg, Q 5. 'Has your fatiguing illness substantially limited your social activities?' 'Yes' is an understatement for many patients, 'wiped out social and other activities' would be more accurate. Emphasis on 'fatiguing illness' similarly trivialises the disease. Surely, any condition that has all the symptoms listed in the questionnaires is more than a 'fatiguing illness'.

Thank you for the opportunity to comment. [...]

[...]

Please find attached my submission for the ME/CFS Common Data Elements Public Review

[...]

Subgroup	CDE, Case Report Form or Measure	Suggested Change	Rationale
All Post-exertional malaise	PEM-focused Studies CRF	The PEM-focused Studies CRF provides guidance on 'Confounding Activity and PEM'. This guidance should also be considered by all other subgroups for inclusion in recommendations for their domains.	<p>The Draft Recommendations for the Post-Exertional Malaise Subgroup include instructions and guidance on 'Confounding Activity and PEM' which attempt to guard against spontaneous activity by subjects affecting measurements in PEM-focused studies. However, PEM has been shown to affect patient physiology in many ways eg. symptoms, cardiorespiratory responses to exercise, pain regulation, immune function markers and possibly gut microbiome*. This means that physiological variables measured in any of the areas under consideration by other subgroups of the CDE Working Group could be significantly affected by PEM. Therefore similar guidance should be considered for inclusion in their recommendations as well.</p> <p>* See the introduction to 'Neural consequences of post-exertion malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome', Dane B. Cook et al., https://doi.org/10.1016/j.bbi.2017.02.009 For a list of studies demonstrating</p>

			effects on these domains in response to acute exercise.
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[...]

A few more comments are attached for the respective groups to consider.

Many thanks

Best

wishes [...]

Subgroup	CDE, Case Report Form or Measure	Suggested Change	Rationale
disability	RAND-36	suggest change to highly recommended	widely used well validated measure and freely available now
immune	medical history and physical exam	many of the questions are not relevant for immune system and are included as part of core, and can be deleted to avoid duplication	avoid duplication and lack of relevance
immune	Rome criteria for IBS and visual symptoms	right at the begining, boxes for AND and OR not necessary; is IBS assumed to be immune related / there are many examples of symptoms that may be best not in the immune category, another example could be optic neuritis relevant in	now clear why this is part of immune system, avoid overloading questionnaires

		ME/CFS and immune related in me/cfs?	
immune	medical history and physical exam	sugggest questionnaire which can be self-completed	the version is only suitable for medical professionals, not for self-completion by patients, a simplified version for patient use would be useful, esp. For population/community use
endocrine	sex hormones	please specify if all tests to be used in both men and women	
endocrine	endocrine lab tests	*Element is classified as Core **Element is classified as Exploratory; this means only TSH is core, what about all tests with no asterisk (*)?	
autonomic	compass-31	a copy of the instrument would be useful	to enable comments

[...]

Dear National Institute of Neurological Disorders and Stroke (NINDS)/Centers for Disease Control and Prevention (CDC), CDE Team Director,

I am writing to provide personal feedback regarding the Public Review Period for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): [Post-Exertional Malaise Subgroup Draft Recommendations](#)

I am [...] patient who has been diagnosed with ME/CFS since June 2015 and now reside in [...]. I am the [...]. The following comments are my personal ones, rather than as a representative of the support group.

A) Areas needed for future research and development

1. Studies of PEM in severely ill patients, children, the elderly, ethnic minorities, and other underrepresented groups.
2. Studies to identify and validate a biomarker(s) that correlates with PEM
3. Studies of treatments to prevent, stop, or mitigate PEM. This includes both behavioral measures, such as balancing activity with rest (commonly termed "pacing"), pharmacologic treatments and integrative/complementary medicine treatments (e.g. yoga, meditation, tai chi, naturopathy, massage).

B) PEM naming

Post-Exertional Malaise (PEM) should be renamed to a term that more accurately reflects the severity of PEM since 'malaise' sounds too mild and does not reflect the extreme symptoms that many people face during what many have termed as a 'crash'. Consequently, many ME/CFS sufferers continue to face trivialization of their symptoms. Some suggested names include: "Post- Exertional Functionality Cessation"; "Post-Exertional Crash".

Yours, [...]

[...]

Perhaps my comments are already incorporated; if so, I missed them. [...]

Subgroup	CDE, Case Report Form or Measure	Suggested Change
biomarkers and others	all that entail blood collection	Suggest precise product source and lot #; e.g. BD Vacutainer® UltraTouch™ push button blood collection set catalog # 367365. For plasma, suggest precise anticoagulant and vacutainer catalog #.
biomarkers and others	all that entail blood collection	As noted in the recommended reading "Preanalytical Variables Affecting the Integrity of Human Biospecimens in Biobanking" by Christina Ellervik and Jim Vaught, Clinical Chemistry 61:7 914–934 (2015), immediate creation of sub aliquots is important. The precise, sterile, endotoxin-free storage vial, suggested volumes and storage temperature all need to be specified.

[...]

Dear Working Group,

May I make your life just a bit easier?

You hardly need bother to consider the merits of the Chalder Fatigue

Scale as a CDE. It has no merits whatsoever.

I was utterly shocked to examine it, which I did for the first time quite recently. That once-brilliant British science should have fallen so far!

There is nothing scientific about this scale. It is not capable of accurate measurement of any symptom. It is not capable of reproducible measurements. It can only measure moderate impairment, not the severe impairments common in this disease.

The Chalder scale will never allow accurate comparison of any one person's characteristics to those of anyone else, let alone allow comparability or meta-analysis across trials.

This is because the scale's fatal underlying deficiency is that its authors were (and remain) determined to prove that "cfs" was (is) a psychological rather than biological disease, and that it could be remediated only with the psychological treatments they have long offered — CBT and GET. The 9000 peer-reviewed papers indicating otherwise can be discussed elsewhere.

Thus, the Chalder scale was contrived to support this fantastical and disproved concept.* In sharp contrast, the Working Group's task is to assure that scientists and physicians operating in the real world have to hand useful scales, which have been designed to measure individual experiences of symptoms that result from underlying metabolic insufficiencies and biological dysfunctions.

Please keep in mind the Chalder scale is totally incapable of taking any measure of what researchers and clinicians need to measure (for varying ends) in patients and research cohorts in respect of ME — individuals' experience of the underlying metabolic insufficiencies causing symptoms in ME.

Thank you for your kind attention in this matter. Sincerely, [...]

* No doubt some persons may wonder how the Chalder scale and other work by persons highly ranked in British academia and professional circles can be characterized as "fantastical and disproved." A full answer would require a very, very long explication of British society, politics, culture, press, class consciousness and more. A short answer might refer to the underlying causes of the American Revolution and our "two great nations separated by a common language."

[...]

The US NIH has released a proposal for Common Data Elements for ME/CFS and asked for public feedback.

Our key messages, which have implications in Canada:

- **Valuable work has been done, but the ME/CFS CDE proposal is not yet ready for full implementation. Key issues should be identified and resolved quickly.**
- **ME/CFS needs to be incorporated into administrative systems and surveys and well as into patient records.**
- **Lessons learned in this initiative should be applied to Fibromyalgia as well.**

The NIH (specifically the National Institute of Neurological Disorders and Stroke (NINDS)) has led a project to develop common data elements (CDEs) for ME/CFS. A proposed set of CDEs and tools was recently released. Feedback was requested on or before January 31.

Work undertaken at NIH affects people all around the world including in Canada. This project could have additional impact in Canada because of collaboration between CIHR and NIH on ME/CFS issues. We are addressing our comments to CIHR as well as to the CDE team.

As you are aware, the National ME/FM Action Network is a patient-based organization that has been working on behalf of Canadians with ME/CFS, FM or both since 1993. We know the history of ME/CFS and FM and the current state of ME/CFS and FM services in Canada. We also have expertise in statistics.

We recognize the value of developing common data elements for ME/CFS. We wish to thank NIH (and NINDS in particular) for leading this initiative and to thank all the people who have contributed to the project. The team has tackled a very challenging area and has done an remarkable job of exploring important issues and proposing variables and measurement instruments. There will undoubtedly be better research coordination because of the dialogue that has taken place.

Nevertheless we find that the proposal contains too many ideas, too little integration of the ideas, too little discussion around how the various instruments would be used, too little examination of response burden for patients and clinicians, and too little testing on how well the instruments work for measurement of ME/CFS. Even recognizing that CDE's are living documents which evolve with time, there is quite a bit of work needed to before the proposal is implemented.

We do not want to see ME/CFS research or research funding delayed while these CDE's are being polished. The situation on the ground is far too serious. An analogy would be to delay sending relief aid to an earthquake zone because the reporting requirements of the relief teams had not been fully developed.

Neither do we want to see ME/CFS research flying off in the wrong direction or in all directions. Decades have been wasted because public policy has leaned toward the wrong model of ME/CFS, one that emphasized psychological factors while de-emphasizing biological factors. Very good analysis has been done on why this was able to happen, and a leading reason was case definitions that were so broad that they included patients with other conditions. Unfortunately, research findings based on the combined group have been inappropriately applied to ME/CFS and this has been very harmful. Case definitions have to be carefully considered. It seems obvious to us that someone who responds poorly to exertion should be treated differently than someone who responds well to exertion and thus we think these are different research domains. For case definition, we favour the Canadian Consensus Criteria not simply because we were instrumental in its development. We believe it does an excellent job of describing the ME/CFS cohort, it requires post-exertional malaise, and it specifies exclusionary conditions.

It is our hope that the ME/CFS CDE team will reconvene, articulate the purpose of the research, identify the key areas that need common measurement and address those areas as quickly as possible. The remaining CDE issues can be addressed over time.

We would like to step back and look at how the CDE project fits into the overall ME/CFS research program.

The ME/CFS CDE initiative seems to be focusing on the content of patient records. The purpose seems to be around research into biological cause and biomarkers. It is not even clear whether the use of the ME/CFS CDE's in clinical trials is being considered as well. If that is the case, then sensitivity to changes over time becomes an important attribute when evaluating variables.

There are other ME/CFS research questions that need to be investigated using data, notably around health and disability administration. These needs are not being addressed by the current CDE project. Data sources for this research would include administrative data and surveys. ME/CFS data elements need to be incorporated into the administrative systems and survey frameworks to yield useful statistics. Standardization would foster comparability between jurisdictions.

Ontario has an initiative underway to provide health care to Ontarians with ME/CFS, FM and MCS. The Ontario Task Force has the advantage of data from the Canadian Community Health Survey which helps define the needs. Among other recommendations, the Task Force has pointed out the need for billing codes. Depending on how this is implemented, the billing database would be a valuable source of data on topics like prevalence, incidence, resource utilization and maybe even co-morbidities. The billing system is not the only possible source of administrative data. Coding for ME/CFS rightly belongs in administrative data files for clinics, hospitals, home care providers, care facilities and first responders where it could be used for research. Standardizing across jurisdictions would allow inter-jurisdictional comparison research.

A different statistical issue that our organization repeatedly encounters is in the realm of disability. Disability can be described in three ways, through a list of impairments in functioning, through a list of activities one cannot do, and through reduced ability to participate. We have noted serious problems in the categories of impairment and activity limitation that are used in disability programs and surveys. Impairment is generally thought of as mapping to a specific activity. People with mild or moderate ME/CFS may be technically able to do all the activities on the activity list but they have to limit the quantity or frequency of activities. The variability and unpredictability of ME/CFS can make planning

even those activities difficult. We are finding many disability surveys and programs based on impairment to be non-inclusive of ME/CFS because they do not list reduced activity levels as an impairment. We find that many surveys and programs based on activities to be non-inclusive of ME/CFS because they demand inability to do particular activities.

Until the classification systems are fixed, the disability survey or program cannot be used for ME/CFS research. There are international initiatives to develop common data elements for disability including the WHO's International Classification of Functioning, Health and Disability (ICF), the InterRAI Home Care Assessment questionnaire and the Washington Group sets of disability questions. The ME/CFS perspective is poorly represented in all three. Until these issues are resolved, ME/CFS will have poor data in the disability area, very much hampering research.

Incorporating ME/CFS data elements into health and disability survey and program data frameworks is important. Is this an extension of the CDE project or is this a new project? Either way, action is needed.

To summarize, we would like a ME/CFS research program that is

- **Targetted:** Research about ME/CFS should be based on a well defined cohort (our recommendation is to use the Canadian Consensus Criteria) and it should be clearly assumed that ME/CFS has a biological basis (and not simply a problem of deconditioning)

and attitudes).

- **Holistic:** Research should cover a range of issues including cause and biomarkers, clinical trials, health services and policy, and disability services and policy.
- **Aggressive:** Estimates of fair funding run into the hundreds of millions of dollars a year in the US and into the tens of millions of dollars a year in Canada, without even taking retroactive entitlement into account. The community is suffering because of research under-funding.
- **Strategic:** With no time to lose, research should be well coordinated.

We believe that the current ME/CFS CDE initiative make an important contribution to ME/CFS research by attempting to maximize the research usefulness of patient records.

We also see the need for ME/CFS data elements to be incorporated into administrative systems and surveys on a consistent basis to ensure availability and comparability for research purposes.

As a final note, let us remind you that the National ME/FM Action Network works on behalf of Canadians with Fibromyalgia as well. We are watching ME/CFS research developments very closely. We hope that a complementary research program for FM will be established as soon as possible and that FM be considered when dealing with health and disability administrative systems and surveys.

[...]

National ME/FM Action Network

[...]

MEadvocacy's concern is that the current NINDS/CDC CDEs draft will not accomplish its intent because:

- they do not specify the research criteria to be used across all federally funded studies (i.e., the ICC)
- they rely on subjective questionnaires most of which were not created for the distinct disease ME
- PEM/PENE, the hallmark feature of ME, is very poorly defined.

I endorse MEadvocacy's recommendations.

- All federally funded researchers use the ICC which was created by ME experts for diagnostic and research purposes.
- New questionnaires be designed which are strictly created with ME patients in mind.
- PENE be strictly defined as per ICC in order to weed out those who suffer from fatiguing conditions - not ME

Thank you for taking the time to do this right. Millions of lives, including our devastatingly ill son, depends upon it.

[...]

[...]

I support MEadvocacy recommendations according to their blog. Thank you,

[...]

[...]

Feedback Details: Topic:

Content of CDEs

Subject: Comment on CDE

Page: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome CDE Standards

Comments:

Several comments (from an informed recently diagnosed patient), No mention of feeling of feverishness. Some ME patients, like myself, experience a below average body temperature with the sensation of extreme feverishness. Questions do not reflect longitudinal nature of the illness. The symptoms expressed in the last 6 months do not represent the degree of variability and morphology of a symptom subset. These symptoms can progress or oscillate in a matter of hours, days, weeks or months. A document that reflects the degree of variability and a timescale will be helpful. IE, Trend, Period, mean and standard deviation of measured data as well as subjective questions. I believe defining this temporal nature is key for this illness. Suggestion, Maybe the linear analog scale should include a second time axis of two years, this would provide a more relevant information that would address my previous point.

[...]

Hello, I am writing to express my strong support for the following recommendations put for by MEAdvocacy:

- All federally funded researchers use the ICC which was created by ME experts for diagnostic and research purposes.
- New questionnaires be designed which are strictly created with ME patients in mind.

- PENE be strictly defined as per ICC in order to weed out those who suffer from fatiguing conditions - not ME

http://www.meadvocacy.org/meadvocacy_s_comment_to_ninds_cdc_cdes_draft_see_what_you_can_do

Sincerely,

[...]

[...]

I am not well enough to sufficiently articulate what needs to be understood concerning the CDEs for ME research. ME Advocacy has done an excellent job of articulating my concerns. Please take their research based comments as my submission. Do not make this horrible disease worse by perpetuating bad science, bad research, and bad policy.

http://www.meadvocacy.org/meadvocacy_s_comment_to_ninds_cdc_cdes_draft_see_what_you_can_do

Thank you. Best regards,

[...]

[...]

I endorse MEAdvocacy's position and wonder why, after 30 years of failure, our government cannot - and will not - accept the published definition of ME and thus make the research useable.

[...]

[...]

The following is submission for Public Review Period for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) CDEs: Deadline of January 31, 2018

MEadvocacy's Concerns

MEadvocacy.org has vigorously advocated for the adoption and use of criteria created by ME experts, like the International Consensus Criteria (ICC), for selecting individuals for research. The aspired goal is to make sure the cohorts being studied include patients who suffer from the same disease (ME) - in exclusion of those suffering from other conditions or idiopathic fatigue.

Broad criteria created by the CDC like the 1994 Fukuda or 2015 IOM do not ensure patient

selection will exclude those who suffer from other fatigue-inducing illnesses. (as shown by Leonard Jason and Frank Twisk published works)

An expectation that the common data elements (CDEs) would be based on clearly defined patient populations does not appear to be met by the current CDE draft because NIH/CDC does not require a specific research criterion to be used for all the federally funded studies. Additionally, the CDEs are too vague in their description of post-exertional malaise (PEM) thus risking inclusion of patients with other diseases in studies for ME.

Background

MEadvocacy.org represents patients who fit the experts' criteria such as the International Consensus Criteria (ICC) for myalgic encephalomyelitis - including the severely ill. In reviewing the proposed common data elements, they fail to accurately select a true ME population. The conflation of persons with ME (pwME-ICC) with persons suffering from conditions with similar symptoms such as CFS, fibromyalgia, postural orthostatic tachycardia syndrome (POTS), Ehlers-Danlos syndromes (EDS), depression or idiopathic fatigue will confuse study results which will only cloud and continue to stunt scientific advancements of the disease ME.

Historically, ME as defined by the ICC has been buried under CDC overly broad definitions such as Holmes, Reeves, Fukuda and most recently IOM. Additionally, the US government health agencies have refused to adopt definitions created by actual ME experts with extensive hands-on experience in treating and researching the disease. This government refusal to recognize ME has caused a lack of research in the exclusive #pwME-ICC (#MEICC) population. The proposed CDEs further aggravate the problem, because they leave it up to the researcher to pick any research criteria of their choosing. Thus, the ME population will again not be clearly identifiable within the broader CFS patient population.

In their draft, the CDE working group for PEM acknowledges they neglected the severe population. They state: "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."

CDEs Do Not Replace Case Definition

NINDS and CDC do not recommend which research definitions federally funded ME researchers should use. In their CDE description, they state:

"Researchers conducting the studies using CDEs will determine the case definition and enrollment criteria that best fit their research objectives. The CDEs are methods of collecting data in a standardized manner... The intention is that CDEs will be applicable independent of the research case definition."

This is an extremely troubling statement from NIH/CDC!

They are advising federally granted researchers to choose whichever enrollment criteria they wish to use. They state: "whichever criteria best fit their research objectives" - so if, for example, they want to show GET is good for pwME, that's fine - just use the inadequate Reeve's criteria!

The CDEs are meant to serve as a method of collecting unified data in a standardized manner, independent of criteria. The real issue here is if the data is taken from cohorts that do not suffer from ME, what disease is NIH/CDC looking at with their CDEs?

The CDE PEM Draft

Since PEM (or more accurately, PENE) is the hallmark and distinctive symptom of an ME diagnosis, great care should be taken in its description and definition. Yet, the current CDEs define PEM as a positive finding of only 1 of the following 5 questions taken from the DSQ questionnaire. (with a moderate severity and frequency)

Dead, heavy feeling after starting to exercise
Next day soreness or fatigue after non-strenuous, everyday activities
Mentally tired after the slightest effort
Minimum exercise makes you physically tired
Physically drained or sick after mild activity

Any one of these questions can be applied to many other illnesses or basically be a result of deconditioning. They do not define PEM per the Canadian Consensus Criteria (CC) nor Post-Exertional Neuroimmune Exhaustion (PENE), in the International Consensus Criteria (ICC) which require a much more significant impact on daily living and is a unique experience seen in ME.

Recommendations

The ICC was created by ME experts for diagnostic and research purposes. The IC Primer lists many recommendations for biological tests to be taken to confirm a proper ME diagnosis - not simply relying on subjective questionnaires.

The goals of the CDEs are admirable but, it can only be effective if the data being looked at and shared are actually based on the distinct disease being discussed. For example, if the CDEs were used to compare ME with major depressive disorders (MDD) and the ME cohort mistakenly included those suffering from MDD and not ME - it will skew the picture.

MEadvocacy's concern is that the current NINDS/CDC CDEs draft will not accomplish its

intent because: they do not specify the research criteria to be used across all federally

funded studies (i.e the ICC)

they rely on subjective questionnaires most of which were not created for the distinct disease ME PEM/PENE, the hallmark feature of ME, is very poorly

defined. Therefore, MEadvocacy recommends that:

All federally funded researchers use the ICC which was created by ME experts for diagnostic and research purposes.

New questionnaires be designed which are strictly created with ME patients in mind.

PENE be strictly defined as per ICC in order to weed out those who suffer from fatiguing conditions

- not ME Thank you for considering our comments in your review process.

[...]

Link to blog:

http://www.meadvocacy.org/meadvocacy_s_comment_to_ninds_cdc_cdes_draft_see_what_you_can_do

[...]

I support the use of ICC and MEAdvocacy's recommendations to use ICC criteria for your research centers. I'm a person with ME for over 20 years per ICC. Currently bed/house bound. USING ANY OTHER CRITERIA WILL MUDDY THE RESEARCH AND CREATE MORE PROBLEMS FOR DIAGNOSIS AND MUCH NEEDED FUNDING FOR THIS DEBILITATING DISEASE!
HOW CAN YOU COMPARE RESEARCH IF THE CENTERS GET TO CHOOSE WHAT CRITERIA THEY WANT TO USE???
PLEASE, WE NEED HELP NOT MORE ROADBLOCKS!

[...]

To Whom it May Concern,

As both a taxpayer and a person who meets every symptom in the ICC for ME, I'm asking you to specify the use of ICC for any research paid for with my tax dollars.

Please end the decades of suffering by people with ME due to studies made useless by incorrect criteria. Dismissive and ignorant doctors, combined with studies that go nowhere due to faulty criteria, leave ME sufferers little hope and increase the incidence of suicide dramatically.

As a sufferer since 2016, my health is deteriorating quickly and my financial resources are bleeding out. I'm alone, housebound, and often bed bound. I would like to work, as opposed to descend into poverty and eventually live on an unlivable amount of disability payments once my savings is gone. Suicide is definitely an option. Treatment is urgent.

Further, please encourage doctors with patients who do not meet the ICC to aggressively search for the cause of patient fatigue.

Please read the attached link—I agree with all points therein.

http://www.meadvocacy.org/meadvocacy_s_comment_to_ninds_cdc_cdes_draft_see_what_you_can_d

[o](#)

Sincerely,

[...]

[...]

PLEASE, I am too sick to articulate what needs to be understood. MEadvocacy has done the work.

Please read these clear research based comments. Do not make a horrible disease worse by perpetuating bad science, bad research, and bad policy.

http://www.meadvocacy.org/meadvocacy_s_comment_to_ninds_cdc_cdes_draft_see_what_you_can_d

[o](#)

Sincerely,

[...]

[...]

ME is not CFS

If studies are to be done on ME they must use criteria that select ME patients and ONLY ME patients, not CFS patients who could in reality have any one of a number of fatiguing conditions, otherwise they are meaningless.

If anyone fits the ICC definition then they have ME. All people with ME will fit all CFS definitions, but by no means all of them with CFS will fit the ICC definition of ME. This is because ME is everything under every CFS definition/criteria PLUS much more.

I wish I could explain this clearly enough but as an ME sufferer for 30 years, I am too severely ill to do so. However, ME Advocacy have produced a very clear response to this proposal and I wish to make it known that I wholeheartedly agree with their submission as I also believe your proposal will make things even worse for ICC ME patients than they already are. And I didn't think that was possible!

Therefore please take their research based comments as my submission. Research based on 'whatever fits the case I want to prove' is not science, let alone good science. Please don't sully the name of good science or harm a very very sick patient community any further.

http://www.meadvocacy.org/meadvocacy_s_comment_to_ninds_cdc_cdes_draft_see_what_you_can_do

Thank you.

Kind regards

[...]

[...]

I am attaching the little I was able to read closely - perhaps I'll send more tomorrow. Good luck to you all.

I was very impressed with all the work and careful thought that has gone into the pages I was able to read. Each of you who worked on this is my hero. It was a daunting task and it'll be great if the same degree of care goes into the final version. It's hard to believe there'll be something final to read in February. This is a huge job.

[...]

I am a patient (with relapsing and remitting, waxing and waning symptoms) since 1965 after

Mono my first semester of college. I am now 70 years old; mostly bed-bound, always house-bound and facing kidney failure. My version seems to be progressive. I hope this Common Data Elements final product will push research, will help to find non-invasive biomarkers leading to cures (or the easing of burdens and pain) for all subsets.

We need a permanent well funded home at the NIH so that clinicians will have a source of information to help take care of us. Even just to deal with individual symptoms as they arise.

Best wishes,

[...]

Subgroup	CDE, Case Report Form or Measure	Suggested Change	Rationale
02 Baseline/Covariate Information	Page 2: General Core questions 3: Ethnicity; 4: Race	Add more subsets which might be of later use in finding a particular ethnicity more prone to ME/CFS	I am of [...] and this makes me susceptible to Breast/Ovarian C
02 Baseline/Covariate Information	Pages 10-11: Rheumatological & Skin Conditions	Add Hidradentis Suppurative, Livedo Reticularis and Alopecia Areata (or just Alopecia)	Have all three; some come and go some all the time. Or could be added to Autoimmune
02 Baseline/Covariate Information	Page 13: Past Surgery	Add Surgical Excision of Swollen Lymph Nodes	For 8 months after removal of my inguinal nodes, all ME/CFS symptoms disappeared
02 Baseline/Covariate Information	Pages 17-19 DSQ - WHY ONLY 6 MONTHS?	There should be a column for longer duration issues that may have receded.	Why limit these issues to previous 6 months; so many of our symptoms was and wane.
02 Baseline/Covariate Information	Page 23 Question 84a	You'll need many more lines for writing current medications	Most of us will need more room
02 Baseline/Covariate Information	Page 29 (and throughout all) Re: C.3 Refers to swollen neck or armpit glands	Add swollen inguinal (groin) glands every time glands are mentioned	For 5 years after Mono, neck glands stuck out, then receded. Now inguinal glands
02 Baseline/Covariate Information	Page 34: Fever (CDC Symptoms should encompass more than past month)	We need a place to note whether our base temperatures are lower than 98.6 normally	My normal temp is 96.8. When I run a fever of 101.8 it is 5 degrees over my 'normal'.
02 Baseline/Covariate Information	Page 47: C.21a	Add more lines.	Many of us will need them.
03 Fatigue Subgroup	Wasn't able to open any of the links		no way to assess any of these

04 Post-Exertional Malaise		The work of Ron Davis at the OMF towards tests that don't destroy the minimal health we enjoy.	I liked the caveats listed. Let's try not to destroy us for months following testing.
05 Sleep Subgroup			So much careful consideration of our different types of sleep disturbance - GREAT
06 Pain Subgroup			Again, hoping Ron Davis and OMF will help. CDC should fund his work.

[...]

Dear NINDS

I received for a time back the draft from NINDNS that was sent to me and a number of other people with a request for comments and feedback to the CDE recommendations.

I am a member of the [...] and lead one of the workgroups in the network. This working group aims to propose criteria and to find standardized methods for symptom mapping and registration of other health information for [...].

We have not completed our task yet and are in the midst of an working process. I have read through the NINDS document and see that there is an overlap regarding the forms proposed by NINDS and suggestions from our working group regarding use of diagnostic criteria as well as topics to be assessed and methods for assessment.

We consider it very important to use DSQ for thorough symptom mapping as you suggest, to get the ability to classify patients based on different case definitions. As long as it is used, it does not really matter what criteria patients satisfy either the CCC, Fukuda or SEID.

In addition, we believe it is mandatory with a comprehensive exclusion investigation to ensure that neither somatic nor psychiatric conditions can explain the symptoms. This is also part of the self-reporting in DSQ, but it is uncertain whether that part of DSQ is good enough. To correct this and because it is often overlap between symptoms such as between fatigue and depression, we therefore suggest that you add a standardized questionnaire that at least records depression and anxiety.

Currently, we have proposed HADS because it is designed to map anxiety and depression in patients admitted to medical departments. What we also know and as many studies in other patient groups have shown are that depression and anxiety increase symptom reporting and intensity and aggravate quality of life. Therefore, we think that an instrument that captures this should be mandatory so that you can control for these factors - anxiety and depression - when doing research on symptoms in the patient group.

Also stress is an important factor in increasing symptom in our patient group – this should also be assessed in one or another way. Perhaps perceived stress scale (PSS) could be an adequate instrument for this purpose.

We appreciate the extensive and useful work you have done. Our working group will look closer into these suggestions and possibly also use some of it in our work and for future proposals [...].

Best regards

[...]

Subgroup	CDE, Case Report Form or Measure	Suggested Change	Rationale
Quality of life	suggest to use HADS (Hospital anxiety and depression scale), could also be another , not too long	adding	make sure that anxiety and depression is not at major level and overlap with ME/CS symptoms, should be controlled for in analysis because it increases symptom reports
Stress	Peceived stress scala (PSS)	adding	increase symptoms and reporting av symptoms , should be assessed and controlled for in analysis

[...]

Thank you. This is decades of neglect and medial abuse. We must get it right this time.

[...]

As someone with M.E. since 1985 who is now Severe (Housebound/Bedbound), I endorse MEadvocacy's recommendations. You have done nothing to help people with M.E. for decades and, apparently, you plan to continue to do nothing useful in the future. My life has been destroyed for 33 years while the CDC has sat around and still sits around covering up the disease, helping no one. It's an utter disgrace and reeks of intentional neglect.

The Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Common Data Elements (CDE) Working Group and the National Institute of Neurological Disorders and Stroke [NINDS]/Centers for Disease Control and Prevention (CDC) CDE Team released their [draft version](#) of the ME/CFS CDEs for public review on 12/15/2017. Public comments are to be submitted by 1/31/2018.

The general NINDS CDE section explains the purpose of the CDEs as follows:

“Many of the CDEs will overlap across study types, which allows for comparisons and meta-analysis across studies. Consistency of the data elements and the CDE formats is kept in order to ensure the ability to transfer critical medical information electronically from one center to another. This consistency also allows for continuity across different disease areas. The goals of the NINDS CDE initiative are to increase the efficiency and effectiveness of clinical research studies and clinical treatment, increase data quality, facilitate data sharing, and help educate new clinical investigators.”

MEadvocacy’s Concerns

MEadvocacy.org has vigorously advocated for the adoption and use of criteria created by ME experts, like the International Consensus Criteria (ICC), for selecting individuals for research. The aspired goal is to make sure the cohorts being studied include patients who suffer from the same

disease (ME) - in exclusion of those suffering from other conditions or idiopathic fatigue.

Broad criteria created by the CDC like the 1994 Fukuda or 2015 IOM do not ensure patient selection will exclude those who suffer from other fatigue-inducing illnesses. (as shown by [Leonard Jason](#) and [Frank Twisk](#) published works)

An expectation that the common data elements (CDEs) would be based on clearly defined patient populations does not appear to be met by the current CDE draft because NIH/CDC does not require a specific research criterion to be used for all the federally funded studies. Additionally, the CDEs are too vague in their description of post-exertional malaise (PEM) thus risking inclusion of patients with other diseases in studies for ME.

Background

MEadvocacy.org represents patients who fit the experts' criteria such as the International Consensus Criteria (ICC) for myalgic encephalomyelitis - including the severely ill. In reviewing the proposed common data elements, they **fail** to accurately select a true ME population. The conflation of persons with ME (pwME-ICC) with persons suffering from conditions with similar symptoms such as CFS, fibromyalgia, postural orthostatic

tachycardia syndrome (POTS), Ehlers-Danlos syndromes (EDS), depression or idiopathic fatigue will confuse study results which will only cloud and continue to stunt scientific advancements of the disease ME.

Historically, ME as defined by the ICC has been buried under CDC overly broad definitions such as Holmes, Reeves, Fukuda and most recently IOM. Additionally, the US government health agencies have refused to adopt definitions created by actual ME experts with extensive hands-on experience in treating and researching the disease. This government refusal to recognize ME has caused a lack of research in the exclusive #pwME-ICC (#MEICC) population. The proposed CDEs further aggravate the problem, because they leave it up to the researcher to pick **any** research criteria of their choosing. Thus, the ME population will again not be clearly identifiable within the broader CFS patient population. In their draft, the CDE working group for PEM **acknowledges they neglected the severe population**. They state: *"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."*

CDEs Do Not Replace Case Definition

NINDS and CDC do not recommend which research definitions federally funded ME researchers should use. In their [CDE description](#), they state:

"Researchers conducting the studies using CDEs will determine the case definition and enrollment criteria that best fit their research objectives. The CDEs are methods of collecting data in a standardized manner... The intention is that CDEs will be applicable independent of the research case definition."

This is an extremely troubling statement from NIH/CDC!

They are advising federally granted researchers to choose whichever enrollment criteria they wish to use. They state: **"whichever criteria best fit their research objectives"** - so if, for example, they want to show GET is good for pwME, that's fine - just use the inadequate Reeve's criteria!

The CDEs are meant to serve as a method of collecting unified data in a standardized manner, independent of criteria. The real issue here is if the data is taken from cohorts that **do not** suffer from ME, what disease is NIH/CDC looking at with their CDEs?

The CDE PEM Draft

Since PEM (or more accurately, PENE) is the hallmark and distinctive symptom of an ME diagnosis, great care should be taken in its description and definition. Yet, the [current CDEs define PEM](#) as a

positive finding of only 1 of the following 5 questions taken from the DSQ questionnaire. (with a moderate severity and frequency)

1. Dead, heavy feeling after starting to exercise
2. Next day soreness or fatigue after non-strenuous, everyday activities
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5. Physically drained or sick after mild activity

Any one of these questions can be applied to many other illnesses or basically be a result of deconditioning. They do not define PEM per the Canadian Consensus Criteria (CCC) nor Post-Exertional Neuroimmune Exhaustion (PENE), in the International Consensus Criteria (ICC) which require a much more significant impact on daily living and is a unique experience seen in ME.

Recommendations

The ICC was created by ME experts for diagnostic **and research** purposes. The [IC Primer](#) lists many recommendations for biological tests to be taken to confirm a proper ME diagnosis - not simply relying on subjective questionnaires.

The goals of the CDEs are admirable but, it can only be effective **if** the data being looked at and shared are actually based on the distinct disease being discussed. For example, if the CDEs were used to compare ME with major depressive disorders (MDD) and the ME cohort mistakenly included those suffering from MDD and not ME - it will skew the picture. MEadvocacy's concern is that the current NINDS/CDC CDEs draft will **not** accomplish its intent because:

- they do not specify the research criteria to be used across all federally funded studies (i.e the ICC)
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- PEM/PENE, the hallmark feature of ME, is very poorly defined.

Therefore, MEadvocacy recommends that:

- **All federally funded researchers use the ICC which was created by ME experts for diagnostic and research purposes.**
- **New questionnaires be designed which are strictly created with ME patients in mind.**
- **PENE be strictly defined as per ICC in order to weed out those who suffer from fatiguing conditions - not ME**

[...]

[...]

Should include simple, exhaled breath analysis since fast and non-invasive:

- 1) Exhaled NO, Nitric oxide, such as from Niox, Siemens or others
- 2) Exhaled hydrocarbons such as by MenssanaResearch.org that have been diagnostic for breast cancer, lung cancer, radiation exposure

Should also include for metabolomics, not just Lactate, but D-Lactate vs L-lactate since D is not made naturally in body and can be poisonous, but can be made in biome.

You should consider adding [...] to the Biomarkers groups since he has both clinical, chemistry, R&D backgrounds for 30 years.

[...]

[...]

To whom this concerns,

I am a [...] and lived an incredibly active lifestyle my entire life. In fact I was bicycling 200 miles weekly when I contracted the flu six weeks after my vaccinations for H1N1 and the routine flu in 2009. Specifically on 12/24/09 I got the flu and never got well again and worse yet, descended into a living hell of brain fog, pain, unimaginable fatigue and a laundry list of other symptoms common to ME victims! I remain confined to my home to this very day constantly seeking with all my heart and soul any possibility of improving my dire condition! It is important that research be conducted using the information already carefully gathered by experts in the field of managing myalgic encephalomyelitis patients! Please stop burying this desperate, patient population in a quagmire of other similar conditions!

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Thank you! Sincerely, [...]

[...]

Hi,

My name is [...]. I am an ME patient and advocate. I blog on [...]. My comment to the CDE draft is in support of the one published by the ME advocacy organization -MEadvocacy, as it appears below:

The Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Common Data Elements (CDE) Working Group and the National Institute of Neurological Disorders and Stroke [NINDS]/Centers for Disease Control and Prevention (CDC) CDE Team released their [draft version](#) of the ME/CFS CDEs for public review on 12/15/2017. Public comments are to be submitted by 1/31/2018.

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Background

MEadvocacy.org represents patients who fit the experts’ criteria such as the International Consensus Criteria (ICC) for myalgic encephalomyelitis - including the severely ill. In reviewing the proposed common data elements, they **fail** to accurately select a true ME population. The conflation of persons with ME (pwME-ICC) with persons suffering from conditions with similar symptoms such as CFS, fibromyalgia, postural orthostatic tachycardia syndrome (POTS), Ehlers-Danlos syndromes (EDS), depression or idiopathic fatigue will confuse study results which will only cloud and continue to stunt scientific advancements of the disease ME.

Historically, ME as defined by the ICC has been buried under CDC overly broad definitions such as Holmes, Reeves, Fukuda and most recently IOM. Additionally, the US government health agencies have refused to adopt definitions created by actual ME experts with extensive hands-on experience in treating and researching the disease. This government refusal to recognize ME has caused a lack of research in the exclusive #pwME-ICC (#MEICC) population. The proposed CDEs further aggravate the problem, because they leave it up to the researcher to pick **any** research criteria of their choosing. Thus, the ME population will again not be clearly identifiable within the broader CFS patient population.

In their draft, the CDE working group for PEM **acknowledges they neglected the severe population**. They state: *“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.”*

CDEs Do Not Replace Case Definition

NINDS and CDC do not recommend which research definitions federally funded ME researchers should use. In their [CDE description](#), they state:

“Researchers conducting the studies using CDEs will determine the case definition and enrollment criteria that best fit their research objectives. The CDEs are methods of collecting data in a standardized manner... The intention is that CDEs will be applicable independent of the research case definition.”

This is an extremely troubling statement from NIH/CDC!

They are advising federally granted researchers to choose whichever enrollment criteria they wish to use. They state: **“whichever criteria best fit their research objectives”** - so if, for example, they want to show GET is good for pwME, that's fine - just use the inadequate Reeve's criteria!

The CDEs are meant to serve as a method of collecting unified data in a standardized manner, independent of criteria. The real issue here is if the data is taken from cohorts that **do not** suffer from ME, what disease is NIH/CDC looking at with their CDEs?

The CDE PEM Draft

Since PEM (or more accurately, PENE) is the hallmark and distinctive symptom of an ME diagnosis, great care should be taken in its description and definition. Yet, the [current CDEs define PEM](#) as a positive finding of only 1 of the following 5 questions taken from the DSQ questionnaire. (with a moderate severity and frequency)

1. Dead, heavy feeling after starting to exercise
2. Next day soreness or fatigue after non-strenuous, everyday activities
3. Mentally tired after the slightest effort
4. Minimum exercise makes you physically tired
5. Physically drained or sick after mild activity

Any one of these questions can be applied to many other illnesses or basically be a result of deconditioning. They do not define PEM per the Canadian Consensus Criteria (CCC) nor Post- Exertional Neuroimmune Exhaustion (PENE), in the International Consensus Criteria (ICC) which require a much more significant impact on daily living and is a unique experience seen in ME.

Recommendations

The ICC was created by ME experts for diagnostic **and research** purposes. The [IC Primer](#) lists many recommendations for biological tests to be taken to confirm a proper ME diagnosis - not simply relying on subjective questionnaires.

The goals of the CDEs are admirable but, it can only be effective **if** the data being looked at and shared are actually based on the distinct disease being discussed. For example, if the CDEs were used to compare ME with major depressive disorders (MDD) and the ME cohort mistakenly included those suffering from MDD and not ME - it will skew the picture.

MEadvocacy's concern is that the current NINDS/CDC CDEs draft will **not** accomplish its intent because:

they do not specify the research criteria to be used across all federally funded studies (i.e the ICC) they rely on subjective questionnaires most of which were not created for the distinct disease ME PEM/PENE, the hallmark feature of ME, is very poorly defined.

Therefore, MEadvocacy recommends that:

All federally funded researchers use the ICC which was created by ME experts for diagnostic and research purposes.

New questionnaires be designed which are strictly created with ME patients in mind.

PENE be strictly defined as per ICC in order to weed out those who suffer from fatiguing conditions - not ME

See, http://www.meadvocacy.org/meadvocacy_s_comment_to_ninds_cdc_cdes_draft_see_what_you_can_do

Very truly yours,

[...]

[...]

I commend the sponsors of the ME/CFS CDE Project and efforts of those who produced the Draft under review.

To improve the effectiveness of this worthwhile Project, I support MEadvocacy's recommendations:
http://www.meadvocacy.org/meadvocacy_s_comment_to_ninds_cdc_cdes_draft_see_what_you_can_do

Regards the need for new questionnaires designed specifically for ME, the "objective" evidence collected and recorded by ME experts and clinicians over the past three decades should be included in the CDE Project. It along with the Biomarkers Subgroup's important recommendation to study ME patients with co- morbid illnesses will guide ME subgrouping and personalized treatment research.

I look forward to reviewing future ME/CFS CDE Drafts. Best regards,

[...]

[...]

Having considerable experience observing sloppy diagnostic methods I agree with MEadvocacy.org's recommendations regarding ME/CFS CDEs. "MEadvocacy.org has vigorously advocated for the adoption and use of criteria created by ME experts, like the International Consensus Criteria (ICC), for selecting individuals for research. The aspired goal is to make sure the cohorts being studied include patients who suffer from the same disease (ME) - in exclusion of those suffering from other conditions or idiopathic fatigue."

[...]

[...]

Hi

Attached are public review comments prepared by a group of patients and advocates. If you have any questions on any of them, let me know and I can contact the authors.

[...]

Cross-Domain Issues for the ME/CFS CDE Recommendations

*Review of Subgroup Materials
Provided by people with ME/CFS
January 31, 2018*

Summary:

The ME/CFS CDE recommendations provide a useful summary of the available instruments and the gaps that need to be addressed and should begin to help to increase cross-study comparability. However, as released for public review, the recommendations have not been adequately integrated across domains and key cross-domain issues still need to be addressed. Examples include the inadequate recording of key case-defining criteria and comorbid/exclusionary diseases, the lack of symptom questionnaires to be used in conjunction with objective instruments in some domains, and the lack of recommendations for reporting harms.

Some of the following recommendations have been addressed in part by domain-specific CDE recommendations and/or in the public comment on those recommendations. The intent of this document is to take a cross-domain perspective in order to identify gaps and/or opportunities to align and rationalize the domain-specific recommendations.

The recommendations below include both immediate needs and longer term needs. The longer term needs will require further research and/or instrument development. The immediate needs are those that can and ideally would be addressed prior to the first release of the CDEs to rationalize instruments across domains and ensure that sufficient information is recorded to enable cross-study comparisons. This includes the following, for which further details are provided in sections 1-9 below:

1. Align and rationalize instruments across domains to reduce instrument/protocol burden and redundancy wherever possible. (Section 8)
2. Provide Core intake forms to be used across all studies that captures information about case defining symptoms, key illnesses, level of severity, and other information such as demographics, duration of disease, type of onset, etc that are required for cross-study comparisons. To achieve this, the following are recommended (Section 2, 3, 6):
 - a. Classify the DSQ instrument as Core, to be used across all studies, to establish a common method of assessing and recording the absence or presence of key case-defining criteria. DSQ also captures other needed information such as duration of disease and type of onset.
 - b. Adopt a Core instrument for use across all studies that records at least key comorbidities that can confound study interpretation and also capture those illnesses that are considered comorbid by some definitions and exclusionary in others.
 - c. Adopt a Core instrument for use across all studies that assesses the patient's level of illness severity (such as Karnofsky).
3. Develop guidance for reporting that requires a) reporting of selection methods and cohort composition, including by key case-defining features, and b) reporting of harms. (Section 5)
4. Develop guidance encouraging researcher correlation of objective measures with subjective symptom experience. (Section 1, 4)
5. Provide guidance to researchers to help them select patients for research. (Section 3)
6. Initiate an immediate effort to comprehensively and qualitatively define the spectrum of disease experience and begin developing methods to capture the dynamicity of patients' symptom status. (Section 2)

1. Guidance for Cross-domain Considerations for Conducting Research in ME/CFS

ME/CFS studies are challenging to design because of the complexity of the disease, the diversity of presentation, the presence of comorbidities, and other factors. Researchers new to the field would likely benefit from a high-level discussion of the considerations that need to be made in designing studies and the instruments to be used in studies. New researchers will also likely need education about the risk of harm to people with ME/CFS from seemingly benign activities and be given guidance on how to design and conduct studies in a way that minimizes the risk of short term PEM or long-lasting disabling harm. It is recommended that a cross-domain guidance document be developed in the next few years that might cover topics such as:

- a. Impact on patients of exertion (e.g. travel to site) and the cognitive/physical demand of the study itself, with the potential for short-term PEM or lasting harm, as well as strategies to minimize the impact of PEM on study outcomes.
- b. Use of pre- and post-test instructions for patients and the need for informed consent in studies using any type of exertion challenge.
- c. Impact of differences in patients' pacing practices on study outcomes and instrument design.
- d. Impact of comorbidities and medications/supplements on different aspects of ME/CFS, with links to information on differential diagnosis of key conditions that could confound study results.
- e. Impact of the waxing and waning of the disease and how to accommodate in the design.
- f. Considerations for designing subsets including e.g. age, gender, acute/non-acute onset, duration of disease, severity, presence or absence of certain comorbid conditions, presence or absence of key case-defining criteria, etc.
- g. Managing/minimizing impact of the study on patients (e.g. filling in forms offline, reducing form length) and accommodating mobility limitations.
- h. Considerations for severely ill patients to ensure that the instruments chosen are appropriate and valid and suggest ways to increase participation of severely ill patients in research studies.
- i. Special considerations for studies in pediatrics.
- j. Importance of using patient reported symptom instruments with objective measures.

Some domains have included guidance that covers some of these points, while other domains, such as the neurocognitive or pain domains, might benefit from such guidance. A high-level cross-domain summary with links to additional sources could cover these points in an integrated fashion across all domains.

2. Developing Our Understanding of Disease Experience

The CDE process and public review has highlighted a continued lack of sufficient clarity and specificity in describing the patient experience of ME/CFS and the consequent ambiguity and diversity in how these terms are used by researchers, clinicians, and patients.

For instance, in recent discussions involving PEM, some focused on exertion as a trigger while others included poor sleep and infections as triggers, as does the IOM report. Do we adequately understand the range of triggering events and the symptoms associated with the experience termed PEM? Similarly, are we clear on the nature and extent of neurological symptoms that people with ME/CFS experience, particularly those who are most severely ill? And fatigue is a common but ill-defined symptom. Do we understand the experience of fatigue in ME/CFS and how it might differ from that in other diseases? These are all questions of how well we understand the patient experience of ME/CFS.

If we lack sufficient clarity and specificity on the patient experience of ME/CFS, then these terms could be interpreted and used differently by different stakeholders and be incorporated into research instruments in ways that don't

adequately capture the disease within and across domains. For instance, the fatigue domain includes post-exertional fatigue as a facet of fatigue but also recommends the Promis instrument which doesn't address post-exertional fatigue. Is post-exertional fatigue part of PEM? Is it a core aspect of fatigue?

This question is not which of these views is correct. The question is about the qualitative patient experience of ME/CFS across the continuum of severity and how we collectively describe and map that experience in the terminology used, the domains of disease, and ultimately the instruments selected to assess the disease. This is not a navel-gazing exercise. ***If we can be more specific and clearer on the qualitative experience of ME/CFS, then we can design better symptom-based instruments and we will be better able to communicate important concepts about this disease in a shared way across researchers, clinicians, and patients. Just as importantly, we can better map objective findings to what the patient is experiencing and know that we are not missing any key features which might change the interpretation of results. This rich and shared language is a foundational element that can expedite progress in research.***

Previous initiatives have focused on understanding the nature of the patient experience. For instance, Dr. Jason has focused on understanding the symptoms that patients experience and translating those into an instrument for case ascertainment. But recent discussions with both patients and researchers indicate that there are still critical gaps and differences in understanding, interpretation, and experience of concepts that are as fundamental to ME/CFS as fatigue and post-exertional malaise. Therefore, an effort is needed to develop a common vocabulary through which patients and researchers may exchange that is grounded in a comprehensive assessment in the patient experience of disease.

We highly recommend that NIH immediately fund and sponsor an initiative of clinicians, researchers, patients, caregivers, and other stakeholders to:

1. More fully evaluate the qualitative patient experience of ME/CFS across domains.
2. Use this to establish and/or refine a formal set of standard definitions of domains and terms.
3. Evaluate currently recommended symptom-based instruments for purpose and suitability for ME/CFS and make recommendations for future development of symptom-based instruments. These symptom-based instruments include at least those for ascertaining cases of ME/CFS in the absence of a biomarker (as discussed in section 3 below) and assessing the subjective experience of the disease as it correlates to objective measures and/or as it changes in response to treatment, exertion, and the fluctuations and progression of the disease over time (as discussed in section 4).

3. Patient Selection: Assessing and Recording Diagnostic Inclusion Criteria and Comorbid/Exclusionary Conditions

Lack of agreement on how patients are selected has been long identified as a key confounder of ME/CFS research and multiple US government reports have prioritized this as a key issue to be resolved. The 2015 Pathways to Prevention Report stated, "variability in inclusion and exclusion criteria, such as the case definition, comorbid conditions, patient population, and disease severity, has significantly hampered progress in the clinical and research domains focused on assessing and treating ME/CFS."

While the CDE initiative was not intended to establish consensus on inclusion/exclusion criteria or on a given case definition, the ME/CFS CDE recommendations published for public review have not classified any instruments as "core" to assess and record the presence or absence of key inclusion criteria across all studies. Recommendations have also not designated a "core" instrument to track conditions that may be considered comorbid by one definition and exclusionary in another. ***Given the diversity of definitions used today (as outlined in the table at the end of this***

document), the lack of common instruments for assessing and recording case-defining criteria and comorbid illnesses across all studies will impede cross-study comparisons. This deficiency could perpetuate the problems noted in the Pathways to Prevention report.

Prior to the March CDE implementation, it is recommended that a “core” instrument be adopted for use across all studies that assesses and records the presence or absence of all key case-defining inclusion criteria. This instrument will need to include assessment questions, a method to score whether the key case-defining criteria are present or not, and data elements to capture that result. While it may lack the desired breadth, it is recommended that the DSQ questionnaire be used as the basis of this instrument because of its breadth and use in the field and lack of a suitable alternative. (The PEM CDE group has recommended a core instrument that uses the DSQ, provides a scoring method, and includes the data element to capture the final determination of PEM that might provide a useful model for other domains to consider). The DSQ questionnaire also collects other critical information such as the date of illness onset and the type of onset that do not appear to be collected elsewhere.

Prior to the March implementation, it is also recommended that a “core” instrument be adopted for use across all studies to capture the presence or absence of at least those conditions that are known to be important confounders and that are treated as comorbid in some case definitions and exclusionary in others. As the Pathways to Prevention report noted, “Carefully defining comorbid conditions is necessary to determine ME/CFS subgroups and move the field forward.” If the Baseline group is going to recommend that the Illnesses Form be made core, this could satisfy this need as long as that form includes all of the key confounding comorbidities/exclusionary conditions.

One of the biggest barriers that makes it difficult to ramp up research and get the pharmaceutical industry involved is the challenge researchers have in identifying patients for their studies. Providing the above plus accompanying guidance on getting patients into research could have a significant impact on this problem.

Together, the instruments for assessing and recording symptoms and for recording comorbid/exclusionary conditions could be part of a “core” intake tool for the interim to be used across all studies.

In the longer term, further research must be funded and undertaken to refine and validate the instruments for assessing the absence or presence of case defining criteria to ensure that this instrument adequately reflects the patient experience of ME/CFS. (See section 2 above)

4. Correlating Objective Measures with Subjective Symptom Reports

In addition to the need for robust symptom-based instruments for case ascertainment, the Institute of Medicine Report noted the importance of correlating subjective reports of symptoms with objective measures. In the absence of an in-depth understanding of the etiology and pathophysiology of ME/CFS, reliance on the patient-reported disease experience is an inevitably critical element of studies which aim to understand the disease pathophysiology, define objective biomarkers, monitor the fluctuations and progression of disease, or determine the effects of an intervention. Until objective measures are validated and biomarkers identified, patient-reported symptoms are all we have to rely upon.

Studies focused on better understanding the basic pathophysiology of the disease mandate comprehensive quantitative measures of patient-reported symptoms to provide context and validation for objective measures. Some domains, such as fatigue, currently rely entirely upon symptom-based instruments and the lack of objective measures puts a premium on these adequately reflecting the disease. The PEM domain calls for both subjective and objective measures but the number of symptoms to be evaluated is low and lacks the needed diversity of patient experience. The neurological, neurocognitive, and biomarker domains specify objective measures but do not appear to provide symptom-based instruments. Apparent exceptions include the mental fatigue scale (neuro) and linear analog scale (immune) but these lack the breadth of relevant symptoms experienced by people with ME/CFS.

In each domain, there is a need for comprehensive symptom-based instruments that are specific to a given domain of illness and quantitatively capture the full range and severity of symptoms associated with that domain. There is also a need for broader, higher level global instruments that can assess symptoms across all domains in order to understand cross-domain interactions and associations. In both cases, these instruments need to accurately reflect the breadth, range and severity of the disease facets. Today, they are either missing or lack the needed specificity, scope, and correlation with the patient experience. This needs to be addressed, as discussed in section 2.

A second requirement is for instrumentation that can assess change in symptoms due to events such as intervention, exertion or other triggering exposure, disease progression and day-to-day fluctuation. Change in symptomology over time is a core feature of ME/CFS yet as a whole the CDE recommendations do not adequately address this issue through study design guidance (e.g. repeating measurements on subsequent days to see the fluctuations) or provision of instruments designed explicitly to quantitatively assess symptom change. The design of the DePaul Symptom Questionnaire, capturing symptoms over the last 6 months, is appropriate for case ascertainment but is not suitable for evaluating short-term change in symptoms.

Instruments such as the linear analog scale within the immune module come closer to the necessary brevity, simplicity, and quantitative nature, but is designed for Fukuda and omits many key symptoms.

Therefore, an urgent need exists for robust, domain-specific and cross-domain instruments that can be used repeatedly to assess patient-reported symptom status within a narrow timeframe (e.g. a single day). These

instruments need to cover the range of symptoms experienced *across all domains*, need to be appropriate and usable for all levels of severity, and need to be low-burden for patients to use (>15 questions on a simple quantitative scale). Such instruments could be used 1) at the individual's baseline (in their home at steady-state), 2) prior to study intervention/assessment (accounting for travel exertion influence), 3) in parallel with objective variable collection (appropriately benchmarking objective values against relative status), and 4) following study intervention (capturing intervention effects, including non-therapeutic interventions such as CPET). Such instruments could also play an important role in distinguishing adverse events from the normal fluctuation of the disease, and bring a more nuanced understanding to studies intended to characterize pathophysiology.

A recent preliminary study tightly associating biologic variables with daily symptom fluctuations (<https://youtu.be/QHlvcw9SNFo>) demonstrates the power of such a frequently administered instrument in leveraging patients' assessment of their physical experience to inform interpretation of subthreshold biometric measures, illustrating the potential of this type of tool in biomarker identification. Utilization of such a cross-domain instrument in the impending longitudinal observational studies would generate a rich dataset enabling subgroup identification and prognostic estimates, and would lay a pivotal foundation for capturing outcome measures in subsequently forthcoming clinical trials.

Whether researchers are evaluating change in symptoms or more generally characterizing the nature of symptoms, it is important for researchers to assess not only the full range of symptoms within their domain of interest, but also symptoms across domains as that could highlight unexpected linkages to other domains. Given the multisystemic nature of ME/CFS, such unanticipated observations will be valuable in discerning pathophysiology and in forming subgroup definitions. Guidance should be supplied for all domains on the importance of correlating patient-reported symptoms with objective measures, and on standards for reporting such analyses.

Development of standardized patient-reported symptom instruments for utilization across and within domains will enable comparability across studies for meta-analysis, transparency in cohort composition, subgroup and biomarker identification, and will lay the foundation for the refinement of potential thresholds for use in cohort definition and trial outcome measure definition. Due to the urgent and critical need, such instruments should be immediately developed by a convened group of ME/CFS experts and patients. Of note, this effort greatly overlaps with that needed for understanding the patient experience of ME/CFS (described in section 2) and the refinement of diagnostic methods (described in section 3), thus capitalization of resources for all three is encouraged. The products of this effort should be aggressively developed and validated in the near term, and ultimately recommended as Core for all CDE domains in their final validated form. In parallel, an RFA for validation of these instruments should be immediately issued. The success of forthcoming patient subgrouping efforts, accurate biomarker identification, and valid clinical trial results depends entirely on the utility of these instruments. It behooves stewards of the limited financial resources allotted to ME/CFS research to recognize and address this need now, before further resources are devoted to efforts which lack the appropriate tools to capture the dynamic ME/CFS disease experience and will inevitably further pollute the literature with varied results from poorly defined cohorts and outcome measures.

Developing these instruments will take time but it is supremely important that researchers combine patient reported symptom questionnaires with objective measures and perform correlation analyses of

the two. For the first release of the CDEs, interim cross-domain guidance (described in section 1) could discuss the importance of this and encourage researchers to use both. The PEM CDE group has discussed the importance of this in its guidance.

5. Developing Comprehensive Reporting Standards

The current CDE recommendations vary widely by domain and generally fall far short on delineation of many critical elements which should be required and/or encouraged to be reported in study publications. Poor transparency in study design has long plagued ME/CFS literature and contributed to the lack of clarity around disease definition. Ensuring adequate reporting of elements such as cohort composition metrics, instrumentation and criteria utilized for cohort selection, and adverse events incurred during study protocols is not only good scientific practice, but particularly important in raising the bar for ME/CFS research with regard to enabling cross-study comparisons and ethical transparency. By setting formal standards and expectations for reporting, the CDE expectations also achieve the effect of ensuring that the required elements remain prominent in researchers' considerations of study design, as well as in their observations throughout protocol execution and data analysis. Thus, this is a venue in which CDE recommendations will dramatically influence researchers' approach and the nature of ME/CFS research for years to come, so careful consideration of the reporting recommendations is warranted during this critical opportunity. It is recommended that reporting of the following elements be considered "core" for all domains:

- a. **Reporting Cohort Composition:** Given the heterogeneity among patients with a ME/CFS diagnosis and the diversity of definitions used, lack of clarity in cohort composition has historically prevented interpretation of mixed results between otherwise comparable studies. To rectify this moving forward, CDE recommendations across all domains must include a requirement for clear reporting of the instruments utilized for patient screening as well as the scoring methods and thresholds utilized for inclusion in study, and any exclusionary criteria. Because the CDE initiative does not include the channeling of these methods into a database, expected standards for reporting methods at publication should be clearly provided to researchers. In addition to instrumentation, thresholds and inclusionary/exclusionary criteria, this report would ideally include a basic breakdown of the percentage of the cohort which met criteria for select case definitions (i.e. Fukuda, CCC, ICC, IOM) and key inclusion criteria (PEM, sleep impairment, etc). A recommendation of the DSQ as a Core screening instrument for cohort selection across all domains would greatly facilitate ease and uniformity in such reporting and is thus strongly warranted. To add further value, CDE recommendations could encourage reporting of subsetted findings stratified by various dimensions, such as key criteria (i.e. total cohort vs. PEM+ only). Additionally, whether subgroups defined by symptoms, duration or severity were selected for or identified during the study analysis is a valuable element of interpretation that should be stated in study results. Exploratory recommendations of specific criteria for such subgroup analyses (i.e. +/- PEM, infectious onset, neurologic features, duration, etc.) could also be developed and deployed by CDE, drawing upon many published reports of notable subgroup features. Lastly, a report of cohort scoring on a Core functional assessment instrument validated in other fatiguing diseases (i.e. WHODAS, Karnofsky, SF-36) would allow readers to gauge relative severity of debility and provide a critical measure of comparability to other disabling diseases, which would ground study findings in a broader medical context and aid in

generating interest in ME/CFS among researchers outside the field. ***Standardization and transparency in precise reporting of these methods will dramatically aid critical review of studies, cross-study comparison and meta-analyses, study reproducibility, and will inform subgroup identification and refinement of the research disease definition and inclusion/exclusion criteria.***

- b. Reporting Adverse Events:** Capturing and reporting adverse events is particularly important due to the potentially permanent damage that can be done to the functional status of a person with ME/CFS through minor exposures to drugs and exertion. Reporting of harms is currently hampered by the lack of an appropriate instrument for measuring patient symptoms following study protocol exposures. The weight of this ethical issue thus further adds urgency to the need for development and deployment of an appropriate instrument. (See section 4 for details on this need.) Nevertheless, CDE recommendations should include guidance on the need to report of harms in any study. This is essential given the low threshold of harm from activities that appear to be benign. As evidenced in section 1, ***anticipating and capturing adverse events in ME/CFS research is a particularly complex issue with many confounding variables, thus special emphasis should be placed on the development of researcher education materials and formal guidelines within the CDE recommendations for all domains.***

6. Critical Cross-Domain Gaps in the Initial Implementation

The domain-specific recommendations that were posted for public review have several critical gaps that must be addressed prior to releasing the first release of CDEs. Some of these recommendations have been included in feedback on the Baseline domain recommendations and it is understood the Baseline group may be doing additional work to address these gaps that was not in the version released for public review. These include the following:

- a. Core ME/CFS Instrument:** An standard interim “core” intake form to be used across all diseases that:
- i. Assesses and records the presence or absence of case-defining criteria. As discussed in Section 3, it is recommended that DSQ questions be used for assessment of symptoms and combined with additional elements that then record whether the key case criteria were present or not.
 - ii. Records the presence of key comorbid/exclusionary conditions as discussed in Section 3.
 - iii. Records other critical information such as demographics, disease onset, duration of disease, etc.

The Baseline group has provided some instruments that could be combined into an intake form but none of these have been classified as core and they may not cover all needed information. A gap analysis will be required to determine what additional elements are needed on a standard intake form.

- b. Core Severity/Functional Instrument:** An interim “core” instrument to be used across all studies to assess and capture the severity of illness from the perspective of functional debility. Illness severity is an important facet of subtyping across all domains and having a consistent method of classifying severity of illness across studies, even if it is basic, will enable cross-study comparison

among

ME/CFS studies as well as comparisons with other disabling diseases (as discussed in section 5a). Due to its longstanding validation, widespread use and simplicity, it is recommended that the Karnofsky scale be utilized for this purpose initially, with the recognition of its limitation in measuring physical but not cognitive debility. In the longer term, consideration could be given to collecting both low-high range and average metrics without a substantial increase in burden. ME/CFS patients can struggle to rank their status as a single value on this scale as their status often fluctuates across a wide range of scores. These combined data would give an adequate picture of the patient's illness severity as well as debility relative to other diseases, and would provide a uniquely valuable picture of the spectrum and fluctuation of debility experience across the ME/CFS population.

7. Critical Cross-domain Gaps Requiring Additional Research

Additional research is needed to address important cross-domain gaps that must be addressed as a priority. Some have been mentioned in the the recommendations of individual domains but are being listed here to emphasize their cross-domain importance and priority.

- a. **Symptom definition & assessment:** As noted above in both sections 2, 3 and 4, further definition of symptom experience and development/validation of symptom-capturing instruments is imperative for a range of needs described. This is a critical need until diagnostic biomarkers are available, but will also be essential to ensure that objective measures reflect and are validated against the patient experience of disease.
- b. **Recovery definition:** A standard definition and method of assessing recovery that represents true recovery and not temporary improvement as has been done in some previous trials.
- c. **Outcome measures:** Robust outcome measures/tools and study designs for assessing change in status as a result of exposures.
 - i. These instruments need to assess multiple dimensions of the disease, include both objective and subjective assessments and meet FDA requirements for drug trials.
 - ii. The same or separate instruments need to also assess change when exertion challenges are used in studies or when assessing the impact of PEM.
 - iii. The recommended instruments must not have floor/ceiling effects that would limit their use across the continuum of severity.
 - iv. Study designs should account for waxing and waning of the disease.
- d. **Harms:** Standards for assessing and reporting harms, especially in treatment trials and in studies involving an exertion challenge.
- e. **Severely Ill:** Further development and validation of all recommended instruments for use in severely ill patients to ensure they are usable, suitable, and valid for that level of severity. Because of issues such as floor effects or demands on the patient, some current instrumentation may not be appropriate across the severity continuum.
- f. **Children:** Further development/evolution and validation of all recommended instruments for use in children.

8. Cross-domain Alignment and Standards

So far, the CDE initiative has focused on domain specific recommendations but has not yet integrated these recommendations across domains. As a result, terminology is not always aligned, the standards for

instrumentation vary, and the recommended instruments have not yet been rationalized to remove redundancy or to fill gaps. Additional focus in the following areas would address these issues:

- a. Align on the definition and alignment of key terms and concepts within and across domains.**
 - i. The word “domain” is used by cognitive. Also NINDS to refer to the type of uses domain as the type of instrument while in most of these CDEs, here “domain” means aspect of illness and the word “subdomain” usually refers to a further breakdown of that.
 - ii. The descriptions of subdomains can overlap across domains and should be rationalized. (e.g. fatigue domain has mental fatigue/cognitive and post-exertional fatigue subdomains which overlap with other domains)
- b. Align and streamline instruments across domains.**
 - i. There is some duplication of instruments across domains that will increase researcher and patient burden and could result in unintended discrepancies. Aligning these would provide a more integrated view and instrumentation of the disease.
- c. Strive for common instrument standards across domains.**
 - i. Suggest instruments that have never been used in ME/CFS before be classified as Exploratory unless there is strong justification for a higher classification, in which case that justification should be stated. Instruments need to be validated specifically in ME/CFS against the patient experience of the disease and should not be considered core until they:
 - ii. Record the specific purpose of each instrument in the summary table in the summary document for each domain.
 - iii. Specify who (e.g. patient, researcher) is expected to fill in the form and expected time to complete. Recommend allow for carer to fill it in if needed unless there is a reason not to.
 - iv. Provide instructions for all instruments.
 - v. Assess design of forms for usability and comprehension.

9. Testing and Implementation

Many of the proposed instruments have never been utilized in ME/CFS research or validated in the ME/CFS population, and many which have been previously utilized contain significant problems with burden (length, complexity, formatting) and wording issues that present challenges unique to the ME/CFS patient. For example, the SF-36 asks: “Did you feel full of pep?” but to ME/CFS patients this is confusing - physical pep or motivational pep? And “Did you feel tired?” - physically tired, mentally tired, sleepy? Instrument wording is a critical element of accurately capturing the ME/CFS experience and patients are often at a loss for how to answer questions given the uniqueness of the disease. This confusion will inevitably lead to noise in the data generated as otherwise similar patients give disparate responses depending on their interpretation of the question or attempts to judge the researcher’s goals. Thus it is highly recommended that the CDE review process include an effort to pilot the instruments selected for use with a group of ME/CFS patients prior to implementation in an effort to identify problems. These issues may then be proactively addressed in the instrument instructions and researchers educated on the potential pitfalls associated with use of the instrument in this patient population. It is also recommended that particular attention be paid to piloting instruments with severely ill patients and caregivers as this population presents a further unique set of constraints. Documentation of the feedback

provided through these efforts could be collected and retained to inform future instrument development and revision efforts as well.

Summary of definitions (Red text shows required symptoms)

This table is intended to demonstrate the diversity of inclusion criteria across definitions that emphasizes the importance of explicitly recording a patient's profile of case-defining criteria to facilitate comparisons across studies. This is a draft summary and would need to be validated for accuracy

Domain	Fukuda	CCC	ME-ICC	IOM	DSQ Q# (1)
Fatigue	Fatigue	Mental, physical fatigue	NA	Fatigue	13, 69,
Timing	> 6 months	> 6 months	NA	> 6 months	6 mon
Impairment	NA	NA?	Substantial reduction in activity	Substantial impairment of function	89-97
PEM	Post-exertional malaise (PEM)	PEM	Post-exertional neuroimmune exhaustion	PEM	14-18, 74-76
Pain	- muscle pain - multi-joint pain - new headaches	Muscles, Joints, headaches	At least one symptom in each of 4 categories: a) pain, b) sleep, c) neurocognitive, & d) neurosensory/perception (e.g. inability to focus vision, sensitivities to light, sound, impaired depth perception), and motor (e.g. muscle weakness, ataxia, lack of coordination, twitching)	Widespread Pain	25-28, 30, 31
Sleep	unrefreshing sleep	Sleep dysfunction		Unrefreshing sleep	19-24
Neurological	NA	Two of neurological or neurocognitive symptoms. Includes ataxia, muscle weakness, vision focus, fasciculations, light, sound sensitivities		NA	34,35, 48, 42, 32, 33 (2), 42(3)
Cognitive	impaired memory or concentration		One of cognitive or orthostatic	36-41, 43,44 41?	
Orthostatic	NA	One symptom of 2 of these 3 categories (also includes sensitivities to food, chemicals, medications	See Energy production and transport		50
Neuro-endocrine	NA		See Energy production and transport	NA	52-60
Immune	- Sore throat - Tender cervical or axillary lymph node		At least one from 3 of 5 categories -flu-like symptoms, susceptibility to infections, GI, GU, sensitivity to meds, chemicals, odors	Sore throat, painful nodes, sensitivity to meds, chemicals, food	61-66
GI, Genito-Urinary	NA	NA		GI, Genito-Urinary	29, 30, 45, 46, 47
Energy Production and Transport	NA	See Neuroendocrine for thermostatic stability, temp intolerance	One symptom of cardiovascular, respiratory, loss of thermostatic stability, intolerance temp extremes	See OI for cardiovascular	50, 51
Symptom requirements	Occurrence	Occurrence	?	Frequency and Severity	Freq & Severity

1) This summary needs to be confirmed

- 2) #32, 33 are muscle twitching, muscle weakness
- 3) #41 – unable to focus vision and/or attention

PEM Domain

*Review of Subgroup Materials
 Provided by people with ME/CFS
 January 31, 2018*

General comments

1. The subgroup’s goals to agree upon an appropriate definition, recommend a standard method for assessment, and to provide standardized recommendations for PEM studies are highly warranted and appropriately defined.
2. Recommendation of the DSQ PEM subscale instrument as CDE Core reflects selection of the best current validated instrument for assessment of PEM as defined by IOM/NAM, however many outstanding issues remain unresolved given use of this instrument. Subgroup recognizes the need for a more robust instrument and that current recommendations are not intended to be permanent, but to bring some standardization to studies in the near term.
3. Acknowledgement of ME/CFS patients’ utilization of pacing methods to prevent/minimize PEM is a critical element both in measuring patient reported experience and in structuring studies aiming to objectively measure PEM.

Key Recommendations

1. Develop and call for funded validation of a PEM-specific instrument which:
 - a. captures the full breadth of patients’ PEM symptom experience,
 - b. quantitatively measures subjective PEM symptom severity,
 - c. is low-burden in length, complexity and wording,
 - d. can be used to screen for PEM experience across a narrow time frame (capturing pre- and post-intervention/exposure status or day-to-day fluctuations)
 - e. accounts for patients’ preventive attempts to minimize PEM,
 - f. accurately distinguishes ME/CFS patients from other comparably disabling disease groups.
2. Standardize scoring methods to achieve objective inclusion (vs. researcher assessment) according to thresholds which account for PEM avoidance behaviors and with adequate sensitivity and specificity to capture a full ME/CFS cohort.
3. Generate guidance for researchers on risk and reporting of harms incurred through study participation.

Summary of Key Recommendations

Current Document	Concern	Recommendation

<p>Use of DSQ PEM Subscale</p>	<p>Validation & specificity: Tested against healthy controls only, not other fatiguing diseases Not validated as a stand alone instrument</p>	<p>Develop and validate an appropriate PEM-specific instrument with validated sensitivity and specificity to distinguish ME/CFS patients from comparably disabled controls.</p>
<p>Use of DSQ subscale</p>	<p>Low sensitivity & ceiling effect: The high scoring threshold necessary to distinguish ME/CFS patients from controls on the DSQ (Murdock 2017) will exclude from studies patients who effectively manage their exertion to avoid PEM and thus report negatively. A more sensitive instrument is needed which accurately captures the full cohort of ME/CFS patients who experience PEM, but may not report as such on the proposed instrument due to their behavioral accommodations.</p>	<p>Develop a more sensitive PEM instrument which accounts for patient behaviors and utilize scoring thresholds that include patients who are capable of experiencing PEM but manage their exertion well.</p>
<p>Use of DSQ subscale</p>	<p>Timeframe: Currently worded to assess a 6-month timeframe, questions fail to assess patients' PEM experience on a time scale that is appropriate for its use in interventional PEM studies. This shortcoming could result in variability among researcher-developed instruments which attempt to capture the near-term patient experience in PEM studies and thus an absence of standardized comparability across studies.</p>	<p>Develop a low-burden PEM instrument which quantitatively assesses symptoms across a timeframe which is useful for pre- peri- and post- intervention assessments in PEM studies (i.e. daily for 3-10 days). In the near term recommendations, advise repeat usage of the DSQ subscale to gauge PEM severity over time.</p>

<p>Cohort composition</p>	<p>Scoring standardization: Reliance upon researcher’s subjective judgement for scoring introduces bias and inconsistency across studies.</p>	<p>Define an objective scoring method for the CDE Core PEM instrument which:</p> <ol style="list-style-type: none"> 1) accurately distinguishes ME/CFS patients from fatigued controls, 2) establishes standardized thresholds for study inclusion, 3) grades PEM severity for more finely-tuned PEM studies. <p>In the near term, provide extensive guidance to researchers on appropriate methods of assessing patient responses to ensure a clean cohort.</p>
<p>Use of DSQ subscale</p>	<p>Symptoms: Questions fail to fully encompass the spectrum of patients’ PEM experience. In addition to failing to measure the full diversity of PEM symptoms, this shortcoming will result in variability among researcher-developed instruments in PEM studies and thus an absence of standardized comparability across studies.</p>	<p>Develop an instrument which more comprehensively interrogates the breadth of symptoms experienced in PEM.</p>
<p>Study design</p>	<p>Confounding exertion management effects: Recommendations fail to adequately educate researchers about and measure the degree to which patient behaviors impact their reported PEM experience. This is a vital element of PEM assessment and must be appropriately captured via instrumentation in order to generate accurate and robust study results.</p>	<p>Include consideration/interrogations of patients’ pacing/avoidance behavior, degree to which lifestyle is limited to avoid PEM, etc. to adequately contextualize patients’ PEM scoring and account for influences which may generate variable results among otherwise comparable patients.</p>

Harms reduction	<p>Potential for harms:</p> <p>The ME/CFS population is particularly vulnerable to lasting harm due to study participation at exceptionally low thresholds of activity. The current recommendations do not adequately advise researchers on this issue, nor do they require monitoring and reporting of adverse events associated with study participation.</p>	<p>Issue extensive educational guidance to researchers on the potential risks to ME/CFS patients of study participation, generating appropriate informed consent, and guidelines for monitoring and reporting of adverse events.</p>
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Immune Domain

*Review of Subgroup Materials
 Provided by people with ME/CFS
 January 31, 2018*

General comments

1. The subgroup very appropriately acknowledges the burden that questionnaire length places on ME/CFS patients and discusses the need for strategies for mitigating these concerns both within the Immune subgroup and across domains.
2. The Medical History Immune module instrument comprehensively assesses immunologically relevant symptomology and comorbidities, providing a valuable data set for analysis that may be used to inform subgroup identification, etiology hypothesis development and prognostic insight.
3. The recommended laboratory tests are generally sufficiently comprehensive and appropriate to the condition, with the exception of the recommended cytokine panel.
4. The subgroup has not provided discussion of the specific inclusion/exclusion criteria or scoring thresholds that will be utilized for cohort selection in immunologic studies. Nor has the subgroup provided discussion of how researchers might explore correlates between objective immunologic metrics and patient-reported symptoms.

Key Recommendations

1. Add a more comprehensive cytokine panel to the recommended laboratory tests, as this is one of the few objective metrics which has a documented association with ME/CFS incidence and severity. The current recommended panel will fail to replicate those key findings, fail to provide an even minimally informative data set, and fail to leverage the full potential of the biological resource being collected.
2. Recommend as Core/Supplementary-HR for all immunologic studies utilization of an instrument which includes a more comprehensive assessment of the patient-reported experience in order to facilitate researcher analysis of correlates between objective immunologic measures and patient-reported symptoms.
3. Include many elements known to be prevalent symptoms and comorbidities among ME/CFS patients which are omitted from the current recommendations.
4. Revise the formatting of the medical history immune module to reduce redundancy and thereby diminish completion burden to the patient.

Summary of Key Recommendations

Current Document	Concern	Recommendation
1. Laboratory tests – cytokine panel	A very limited panel of cytokines is currently recommended for analysis. Given the burden to patients in completing intake instrumentation and blood draw, it is warranted that a more comprehensive analysis be performed to leverage this patient and laboratory resource investment.	As cytokines are one of very few objective measures to have a documented correlation with ME/CFS incidence and severity (Montoya PNAS 2017 PMID: 28760971), the subgroup is strongly encouraged to expand the panel of recommended cytokines to include a more comprehensive assessment of various immunologic axes as well as inclusion of all cytokines with a documented disease association. See notes below for more detail.
2. Medical History Immune module – Linear analogue scale of symptoms over past 6 months	The current recommendation does not supply researchers with sufficient data on ME/CFS patient symptoms to perform an analysis of correlation between objective measures being collected (i.e. cytokines, cell subset frequencies) and patient symptoms. Nor is such an analysis discussed or encouraged in the subgroup’s recommendations.	Recommend as Core or Supplementary-HR for all immunologic studies utilization of the DSQ or other ME/CFS-specific instrument which more comprehensively captures the breadth of symptoms experienced by patients to equip researchers with the data necessary for correlative analysis of objective and subjective measures. Actively recommend such analyses and encourage reporting of findings in immunologic studies.
3. Medical History Immune module instrument – missing conditions	Many immunologically relevant conditions often anecdotally reported by ME/CFS patients are notably absent from this questionnaire. This intake instrument is a critical opportunity to comprehensively capture the breadth of symptoms and comorbidities that occur in	Rectify omitted symptoms/conditions in Medical History Immune module condition lists. See detailed section below (Medical History Missing Elements) for individual conditions to be added to each section.

	ME/CFS patients, thus a	
	more thorough assessment is warranted.	
4. Medical History Immune module - condition lists repeated 3 times in each section	There is high redundancy in sections surveying lists of conditions 3 times consecutively for diagnosis history, active status/medications, and resolved status, requiring patients to read through the same material repetitively and make more cognitive subject leaps than necessary. This places a highly unnecessary burden on the ME/CFS patient which will have physical consequences and will likely lead to reduced completion rate and accuracy.	Prioritize wording brevity and formatting simplicity to reduce redundancy and improve cognitive/time burden for completion. Specifically, change survey formatting to condense identical lists of conditions, moving “ever diagnosed” and “no longer active” into the table surveying “active/medications” so that each condition is listed only once. This allows patients to evaluate each in its entirety and answer diagnosed (with year)/present/resolved and medications in one cognitive step before moving onto the next condition in the list. This will dramatically reduce the volume of reading required, overall survey length and time required to complete. This will allow also for the addition of missing elements (noted below) without increasing overall survey length.

Medical History – Minor Comments & Missing Elements

1. Question 2: “N/V/D” should be spelled out “nausea/vomiting/diarrhea” as the abbreviation is not clear to patients.
2. Adverse drug reactions: Question is vague. Many ME/CFS patients have tried a multitude of medications, often with reactions – they will likely volunteer these anecdotes. If this question aimed only at major anaphylaxis episodes it should be stated as such.
3. Past six months linear analog scale symptoms: Fails to capture fever/night sweats and malaise/flu-like symptoms, which are very relevant metrics for immunologic analysis and likely correlates with objective measures such as certain cytokines or cell subset frequencies. Fails to capture autonomic/orthostatic dysfunction and neurologic sensory features such as hyperacusis/photophobia and fails to adequately capture PEM. This tool is not tailored to the patient experience of disease nor a comprehensive enough survey of the breadth of symptoms experienced in ME/CFS to enable correlative analysis of symptoms with objective measures, an

aim of vital importance in immunologic studies. Additionally, no encouragement or specific guidance is provided for performing analyses which correlate patient symptoms (or subgroups/case criteria/duration/onset/etc.) with objective findings.

4. Year of diagnosis captured for eye conditions, but this field is not listed in other body domain sections. Recommend incorporating this field into a combined table capturing diagnosis history/year/current status/medications/resolved status for each condition in one cognitive step.
5. ENT: Documents tonsillectomy but fails to capture adenectomy/adenoid hypertrophy, common in ME/CFS. Fails to capture tinnitus, vertigo, cervical lymphitis, TMJ, and Bell's palsy, all of which have notably elevated prevalence among ME/CFS patients.
6. LUNG: Fails to capture sarcoidosis, a frequently reported comorbidity in ME/CFS.
7. BLOOD/IMMUNE: Fails to capture hemophagocytic lymphohistiocytosis (HLH) or Hashimoto's thyroiditis, immunologic conditions with many features that overlap ME/CFS. Captures myeloproliferative but not lymphoproliferative disorders, which is particularly problematic given the known association between NHL and ME/CFS. Fails to capture antiphospholipid syndrome, a common comorbidity.
8. INFECTIONS: "Mononucleosis" should also state "EBV, HHV-6" as this is what many patients are aware of in their diagnosis. Fails to capture herpes simplex, enterovirus, coxsackie, Q fever, Ross River.

Table 2A Infectious Disease Laboratory Tests – Serum antibodies

1. Inclusion of HSV-1, HSV-2, and HPV antibody titers is warranted for a comprehensive analysis.

Table 2B Infectious Disease Laboratory Tests – PCR, Other

1. PCR distinguishing both HHV6a and HHV6b subtypes is warranted.

Table 3 Autoimmunological and Other Immune Profiling Laboratory Tests

1. Inclusion of type I IFN (IFNa/b) in cytokines is warranted for a comprehensive analysis and may provide a correlate to viral antibody titers more indicative of an active infectious process.
2. A more comprehensive cytokine panel is strongly warranted, including representatives of major immune axes such as IL23/17, IL4/5/13, IL10, IL-18/1a/b/1ra, IL-2/s2r, leptin, CCL2, GM-CSF, etc. in order for a more valuable data set to be generated from the biomaterials being collected. Given their status as one of the few objective measures of ME/CFS disease severity, cytokines are a vital research component of the blood being collected and it does patients a disservice to omit a comprehensive assay. It is recommended that the subgroup consult published literature to include in this panel all cytokines which have been previously implicated as aberrant in ME/CFS (i.e. CCL11, CXCL1, CXCL10, IFN- γ , IL-4, IL-5, IL-7, IL-12p70, IL-13, IL-17F, leptin, G-CSF, GM-CSF, LIF, NGF, SCF, TGF- α , etc.) as well as consult immunologists to develop a panel which will give a more global view of variations in major immunologic processes. While it is acknowledged that blood volume is a major constraint in these assays, cytokine analysis is such a proven critical element of ME/CFS immunologic research that it warrants development of a sufficient panel given the patient and laboratory research investment already being made to survey the 6 cytokines currently recommended. It would be a shame not

to leverage this investment for a far more informative dataset which could have the potential to replicate existing studies and provide valuable new insight.

Neurologic/Cognitive/CNS Imaging Domain

Review of Subgroup Materials

Provided by people with ME/CFS

January 31, 2018

General comments

1. Extensive list of neurocognitive instruments. Well reviewed, organized, and presented
2. Extensive list of well-organized imaging tools. Good guidance for imaging studies.

Key Recommendations

1. Establish a core instrument to be used across all studies to assess and record the presence or absence of key neurocognitive symptoms as key case defining criteria. Prioritize the development of a core instrument for the range of both neurological and neurocognitive symptoms.
 - o Note: a cross-domain instrument that assesses all key symptoms could address the short term and long term need.
2. Prioritize the development of an instrument(s) to characterize the participant's subjective experience of neurological and neurocognitive manifestations and recommend it/they be used in conjunction with objective instruments in neurological or neurocognitive focused studies.
3. Provide new and/or revised guidance for conducting neurocognitive and neurological focused studies to include information about the importance of using both subjective and objective measures and of managing confounders.
4. Instrument classification: Consider whether instruments that have never been used in ME/CFS should be classified as anything other than exploratory. If warranted, state why and for what purpose and include the lack of use in ME/CFS as a limitation.

Background on Key Recommendations

Current Document	Concern	Recommendation
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<p>1. No core instrument assesses neurocognitive and neurological symptoms as case defining symptoms</p>	<ul style="list-style-type: none"> ● Neurocognitive and neurological symptoms are key case defining symptoms in the IOM, CCC, and ME-ICC definitions and their presence or absence will impact the findings in these studies. ● The only recommended instrument that appears to capture patient reported neurological or neurocognitive symptoms is the mental fatigue scale. But that scale is only 	<ul style="list-style-type: none"> ● Establish a core tool to be used in all studies to assess and record the presence or absence of neurocognitive symptoms as important case defining criteria. The DSQ neurocognitive questions and scoring method are recommended as starting points along with the use of data elements
	<p>partially focused on neurocognitive (3 of 15 questions), appears to assess severity but not frequency, and it's not clear that its been used in ME/CFS.</p> <ul style="list-style-type: none"> ● The DSQ has been used in ME/CFS, captures a broader range of neurocognitive symptoms, and evaluates both symptom frequency and severity as recommended by the IOM 	<p>to capture whether neurocognitive impairment is present or not. (1)</p> <ul style="list-style-type: none"> ● Include a prioritized recommendation for the evolution of the core instrument to fully reflect the range of neurological and neurocognitive symptoms
<p>2. The neurological instruments do not include an instrument to characterize the range of patient reported neurological symptoms.</p> <p>The neurocognitive instruments include the mental fatigue scale but it is not focused on neurocognitive and does not appear to cover the range of patient reported symptoms.</p>	<ul style="list-style-type: none"> ● IOM noted a) both objective and subjective measures are important, b) objective and self-report measures of cognitive impairment do not always concur, and c) one study found that self-reported measures of cognitive impairment were more accurate. ● Characterizing symptoms may provide important context for objective measures. ● Some neurological or neurocognitive manifestations may lack tests and thus require self-report to assess ● Different definitions have differences in the breadth of symptoms included. For instance, Fukuda's description of cognitive impairment is narrower than others ● Neurocognitive and/or neurological focused studies may need instruments that are more comprehensive than the core instrument noted in #1 for case assessment 	<p>Assuming a more comprehensive instrument is needed that that provided for the core instrument:</p> <ul style="list-style-type: none"> ● Include a prioritized recommendation for the development of instruments for use in neurological and neurocognitive focused studies that capture the breadth of patient reported neurological and neurocognitive symptoms. <p>Note: A summary of neurological and neurocognitive symptoms mentioned in key definitions and FDA's Voice of the Patient is provided below for context on this recommendation.</p>

<p>3. Some guidance exists for neurological studies but not for neurocognitive studies</p>	<ul style="list-style-type: none"> ● Guidance can help bring new researchers up to speed quickly and ensure more productivity in research. ● The Neurological guidance is a good start with information on managing the impact of PEM and giving guidance to participants before hand. Potential gaps are a) managing confounding factors such as medication and co-morbid conditions (pain) if needed, b) recommendations to assess patient reported symptoms as well as objective measures, and c) directions to patients post-test if needed 	<ul style="list-style-type: none"> ● Building on the approach taken in the neurological guidance, develop/evolve guidance for both neurological and neurocognitive studies to also include a) managing confounders like PEM, medications, comorbidities if needed, b) the importance of recording both objective and subjective measures, c) any restrictions in severely ill patients ● For neurocognitive, consider whether a CRF is needed to record the presence of comorbid psychiatric illness. See Miscellaneous Comments below.
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1) The PEM CDE core PEM instrument might provide a useful model for this. Note: It would be more integrated and easier to use if a single core instrument were provided to assess and record the presence or absence of all case defining criteria across all studies. But to date, that has not been recommended.

Additional Recommendations, Comments, and Questions

Some of these may require additional research. If so, this could be highlighted in the Summary Section 6 as a gap

1. Instrument descriptions: Some of the instruments do not explicitly state whether the instrument has been used in ME/CFS before. This should be stated explicitly.
2. Illness Severity: Some of the neurological studies have shown correlation of findings with illness severity. Ideally the Baseline or QOL groups will provide a core tool to assess illness severity but if not, recommend that this group implement a common approach to assessing and recording illness severity for use in the neurological studies and if needed the neurocognitive studies
3. Future research: The IOM noted the impact of exertion and orthostatic challenges on cognitive tests but that few studies had examined these. Should the Summary Section 6 (future research) include recommendations to use exertion or orthostatic challenges in these studies? Other future needs to be listed in this section are noted above – a) the need for a core instrument to assess these case defining features of ME/CFS and b) the need for instruments to characterize patient symptoms along with objective measures in neurological and neurocognitive focused studies
4. Psychiatric co-morbidity and subsetting:
 - a. If psychiatric assessment is intended to be part of this domain, will this group also provide guidance/references for screening for these diagnoses?
 - b. Does this group have any recommendations for mental disorders that should be excluded from research studies?
 - c. Should the presence of psychiatric illness be explicitly recorded on a CRF for neurocognitive focused studies, given the IOM comments that differences in co-morbid psychiatric illness might affect neuropsychiatric testing?
5. Rationalize across domains: Both this group and the fatigue group are assessing mental fatigue. Do they have a common definition for this term and common methods?

6. Potential Gap: Does vision belong in this group and if not here, then where? Is neuromotor included?
7. General Comments
 - a. Neurocognitive Overview Summary Table – clarify difference between “Cognitive Subdomains (A)” and Cognitive Subdomains” in the title. Looks like the second column is a break down of the first but the headings don’t clarify that.
 - b. Neurocognitive Overview Section 5 – states “I think” and “in my opinion.” Suggest maybe “we” or “the group,”
 - c. Neurocognitive Overview Summary Table – A brief glossary of the subdomain terms used in this table might help the researcher?
 - d. The patient section was not filled in in the neurological and neurocognitive summaries. Will that be done?
 - e. The Edinburgh Handedness Inventory states this should be used in every neuroimaging study but that doesn’t appear to be listed in the guidance on the neurological section. Should that be added?

Further Details on Key Recommendations

1. Characterizing symptoms in neurocognitive and neurological focused studies

Summary of neurological and neurocognitive symptoms reported across various sources

The following table is a draft summary of the neurological and neurocognitive symptoms reported in the IOM, the key case definitions and the FDA's Voice of the Patient. It is recognized that some of the symptoms classified as neurological by various definitions could have non-neurological causes. Note that this is a draft to demonstrate the range of symptoms and would need to be confirmed.

System/area impacted	List of symptoms	IOM	CCC	2017 Pedi- atric	ME- ICC
Cognitive impairment	Impaired working memory, short term memory	X	X	X	X
Cognitive impairment	Slowed Processing Speed, slowed thought, impaired psychomotor function	X	X	X	X
Cognitive impairment	Decreased/impaired concentration and attention span	X	X	X	X
Cognitive impairment	Difficulty understanding information, expressing thoughts, slowed speech, difficulty doing math	X	X	X	X
Cognitive impairment	Difficulty finding words or numbers, expressive dysphasia	X	X	X	X
Cognitive impairment	Absent-mindedness	X	X	X	
Cognitive impairment	increased distractibility or difficulty paying attention	X	X	X	
Cognitive impairment	Inability to multitask	X	X	X	
Cognitive impairment	Confusion, Disorientation	X	X		X
Cognitive impairment	Dyslexia, inverting words and numbers		X		X
Cognitive impairment	Difficulty making decisions				X
Cognitive impairment	Stuttering				
Cognitive impairment	Lose all sense of how to get from place to place, spatially disoriented, extreme confusion in public places				
Cognitive impairment	Difficulty writing		X		
Neurological	Photophobia - Light sensitivity		X	X	X
Neurological	Touch sensitivity			X	X

Neurological	Hyperacusis - Noise sensitivity	X	X	X	X		X
Neurological	Visual sensitivity						X
Neurological/neuromotor	Poor coordination, instability, imbalance, feeling unsteady on feet, Spatial disorientation and instability, gait tracking, clumsiness, falling	X	X		X		X
Neurological/neuromotor	Seizures						X
Neurological/neuromotor	Twitching, fasciculations		X		X		
Neurological/neuromotor	Ataxia		X		X		X
Neurological/neuromotor	Temporary loss of basic habituated motor programs such as walking		X				
Neurosensory and perceptual (ME-ICC)	Impaired depth perception, loss of depth perception		X		X		
In case these belong in neurological							
Vision	Dimmed vision	X					
Vision	Blurring of vision (listed as OI in pediatric)	X		X			X
Vision	Inability to focus vision and other visual disturbances		X		X		X

Quality of Life/Functional Status/CPET Testing/Activity Domain

Review of Subgroup Materials Provided by people with ME/CFS January 31, 2018

General comments

It would make the materials for this domain easier to understand if the domain summary was available, the specific purpose of each instrument and case report form (CRF) was specified, and instructions for each instrument and CRF were included. Some instruments have this information but not all. Without the additional context, the scope of this domain appears to be a grab bag of leftovers and may be difficult for researchers to effectively use. Because that context was missing, the following comments may reflect a misunderstanding of the domain.

Key Recommendations

1.) Finalize the summary document and instrument information before implementation in order to provide important context and orientation for new researchers on the scope and recommendations for this domain.

- The current summary only includes the responses to the patient advocate questions. Provide responses to the first set of questions.
- Update the summary table (page 2) to designate the purpose of each instrument and to state whether it's appropriate for adults, children or both.
- For those instruments that do not have it, provide instructions and where needed, also a notice of copyright. The instructions should include who is expected to fill it out. The Notice of Copyright should include discussion of its use, validation conducting including specifically in ME/CFS, psychometric properties, strengths and limitations, and references.
- If instruments have not been used in ME/CFS, recommend classifying these as exploratory.
- Provide instructions to researchers on identifying, anticipating and accounting for ME/CFS disease-specific factors and reactions which may impact study results. For example, prior to a CPET study, a patient may anticipatorily undertake a prophylactic IV saline therapy in an effort to reduce their orthostatic intolerance

symptoms during an exertion challenge. This intervention may impact blood volume, which in turn modulates heart rate, resulting in distorted study variable values for that patient relative to a typical hydration state and between patients discordant for the prophylactic intervention.

2.) Establish a "core" instrument to assess the levels of illness severity/functional impairment across all studies in the first release of the QOL CDE.

- Some ME/CFS definitions specify a substantial reduction in activity or substantial decrease in functioning as a case-defining criterion. Further, the level of illness severity is an important subtyping factor and gives important context for the interpretation of study findings. Therefore, a core instrument should be established in the first release to assess this aspect of illness in a common way across all studies.
- SF-36 has been used for assessing the level of functional impairment in some ME/CFS studies and has the advantage of having been used in other diseases. But patients have raised concerns that the SF-36 wording may present challenges unique to the ME/CFS patient. For example, the SF-36 asks: "Did you feel full of pep?" but to ME/CFS patients this is confusing - physical pep or motivational pep? And "Did you feel tired?" - physically tired, mentally tired, sleepy? The appropriateness of SF-36 for ME/CFS needs to be further evaluated.
- If the SF-36 is used, the scoring method must be defined. In the past, the scoring method has varied across studies with at least one study only requiring debility on any one of the eight scales, including on just the "role-emotional" scale. This could result in patients with mental illness who do not have ME/CFS being included in the study. If SF-36 is to be used as the

interim “core” tool to assess the level of functional impairment, it is essential that the scoring method and thresholds for each subscale be specified. For more information on this, see the 2016 article by L. Jason

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5312955/>

- Note that the current SF-36 NOC discusses the SF-36 profile in ME/CFS patients on page 10 but does not discuss this requirement in the scoring section on page 8.

- Karnofsky might be another alternative for an interim core tool to at least rate the level of illness severity from a functional debility perspective. It has been used in ME/CFS and in other diseases. However, it is not a long-term solution as it is a coarse instrument that may not adequately reflect differences in levels of

functioning. Further, it does not provide separate scores for cognitive and physical functioning. Evaluating both types of functioning is important in ME/CFS since these two key aspects of illness do not always track together.

- If neither of these instruments is considered suitable as an interim solution, consider adopting a simple Mild, Moderate, Severe, and Very Severe Scale to classify illness severity in a common way across studies.
- Whatever tool is adopted as an interim solution, additional research is needed to develop and validate a tool or tools that accurately reflect the patient experience of ME/CFS at all ages and levels of severity and that separately score cognitive and physical impairments. The WHODAS appears to do a better job of assessing cognitive impairment and also has the advantage of being used across diseases, but it has not been evaluated in ME/CFS.

3.) Provide Additional Information on the Use and Risks of CPET

- Instructions and CRF:
 - Provide a Notice of Copyright that includes discussion of its use, validation conducting including specifically in ME/CFS, psychometric properties, strengths and limitations (particularly age or severity), and references. This needs to discuss the 2-day form of CPET and include references where the 2-day CPET was used in ME/CFS. If the intent is to recommend both the 1-day and 2-day formats, the rationale for when to choose one test format over the other should be provided.
 - The instructions need to state the need to inform patients of the risk of harm as described below and provide pre- and post-test guidance on how to mitigate against the exacerbation of symptoms and worsening of condition after the test. Instructions should also specify that patients should be monitored for at least 7 days after the test to determine that patients returned to their baseline functioning. If patients have not returned to baseline after 7 days, the researcher should continue to monitor them until they do. If the table on page 20 (part of Question 11) were part of the CPET CRF, this might be useful for this purpose. Alternatively, the questions on page 5 (Exercise Recovery Questionnaire) might be useful or the group might consider questionnaires that also incorporate questions on symptom exacerbation.

- Consider moving just the table on page 20 of Question 11 from the “Physical Functioning and Activities of Daily Living” to the CPET CRF on pages 4-6. This table is not appropriate in the “Physical Functioning and Activities of Daily Living” form because it is specific to the 2-day CPET. Note: It appears that the three questions with numerical scales under the table at Question 11 should remain on the Physical Functioning form.
- Regardless of the location, the table in Question 11 would be easier to comprehend and complete if it were redesigned. As currently laid out, it could be confusing.
- Pediatric use:
 - It does not appear that the 2-day CPET has not been used or validated in pediatric ME/CFS patients. If the standard 1 day CPET has been used in pediatric patients with other diseases, it would be helpful to provide references to those studies as those could provide insight into utility and potential risk of harm. Either way, further research is needed to evaluate the utility and safety of 2-day CPET in pediatric patients. In the meantime, if no studies have been done, this limitation should be noted in the NOC.
- Risk of harm:
 - While CPET is considered the gold standard test for evaluating functional capacity across diseases, CPET is known to exacerbate ME/CFS symptoms at least temporarily. But some patients with ME/CFS have reported longer term harm. The magnitude of this risk and what subgroups are at risk is not currently known. Therefore, patients need to be well-informed of what is currently known about the risk so that they can make an informed risk-benefit decision before undergoing CPET.
 - Unfortunately, little is known about which patients are at risk of long-term impairment from CPET. Further research is needed to understand this and that should be added to the list of future research.
 - Because severely ill patients cannot do CPET, other methods of objectively assessing functional capacity will need to be developed and this could be included on the list of needed research . In the meantime, it would seem appropriate to recommend a tool like the SF-36 for the general assessment of functional impairment (such as the SF-36) while the 2-day CPET is best suited for studies using an exercise challenge to exacerbate the disease. If true, this purpose of the CPET should be explicitly stated in the summary table.

4.) Future Research Needs

- Provide separate instruments that are appropriate for children using language that reflects their activities, functions, and life experiences.

- Ensure that all instruments and the language used therein are specifically appropriate to patients' experiences of ME/CFS, that each instrument covers the full range of illness severity and both cognitive and physical impairment, and that instruments are appropriate for patients who may have been ill with ME/CFS for decades and don't remember previous life experiences.
- Further evaluate the risk of harm including long-term harm to adults and children with ME/CFS from the use of CPET to better predict which patients might be affected.
- Develop objective measures of level of functional impairment that can be used across the continuum of severity.

5.) Additional Tool-Specific Comments

- **General:** In any form that asks about sex, ask about gender instead to allow non-binary responses.
- **SF-36** (page 7): Needs to have a specific scoring method added as noted above in section 2 above, regarding the requirement that debility be more than just emotional debility.
- **Functional Disability Inventory** (page 15):
 - This is rated as supplemental even though it does not appear to have been used or validated in ME/CFS. It should be listed as exploratory if not previously used in ME/CFS unless there is solid justification. That justification should be stated.
- **Physical Functioning and Activities of Daily Living** (page 17):
 - It is unclear where this form came from. Has this been used in ME/CFS before? Has it been validated for ME/CFS? There are numerous potential issues with the way that these questions are asked for this population that suggest that this tool needs further development to make it usable and appropriate for this disease.
 - For instance, on page 17, because of the limited functioning of patients, other items might need to be added such as speaking, cooking, dressing, eating, typing or texting. On pages 17-18, questions 2, 3, 4 and 7 are fatigue-focused. Question 9 combines activities in bed and chair but the orthostatic demand of the two is considerably different in ME/CFS suggesting two separate categories are needed. On page 20, the table at question 11 is specific to the 2-day CPET and doesn't appear to belong. On page 21, the intensity scale on question 12a combines light weights with walking in one question but those may represent a significant range in functioning in ME/CFS patients. These issues call into question the appropriateness of this form for ME/CFS.
 - These concerns should be listed as a limitation in the NOC for this instrument.
 - Needs both instructions and an NOC that discusses where previously used, its psychometric properties including specifically in ME/CFS, its limitations, etc.
 - Some of the questions on this form overlap with questions on the DSQ. If the DSQ were to be adopted as a core

- instrument, might need to rationalize across the DSQ and this to minimize redundancy
- The table at question 11, “Questionnaire for ME/CFS Participants Survey of Activity Level Before and After Two-Day Cardiopulmonary Exercise Tests” appears to be specific to CPET studies. It’s unclear why this table is in the middle of the Physical Functioning form. It’s recommended that the table be moved to the CPET CRF. It’s assumed that the three questions immediately following the table would remain on the Physical Functioning form.
 - **Bell Scale** (page 22): Needs instructions and written discussion of its use, validation including whether specifically validated in ME/CFS, psychometric properties, limitations, etc.
 - **EuroQoL-5** (page 23):
 - The link appears to be broken.
 - The tool may have additional limitations that should be listed.
 1. In the section on self-care, it asks about difficulty bathing but does not account for the significantly reduced frequency of bathing – dictated by the exertion required to bathe and/or repercussions of that exertion.
 2. The same applies to getting dressed. Many people with ME/CFS are rarely in anything other than pajamas because of the exertion required and consequences of changing clothes twice each day.
 - **Health Related Quality of Life-14** (page 29): Some questions are not appropriate for children.
 - **Karnofsky scale** (page 31): Needs instructions and discussion of its use, validation including whether specifically validated in ME/CFS, psychometric properties, limitations, etc. This tool is not appropriate for children and this limitation should be explicitly stated. Ideally, this would be provided through an NOC.

Baseline/Covariate Information Domain

Review of Subgroup Materials

Provided by people with ME/CFS

January 31, 2018

General comments

1. The current Baseline recommendations as provided for public review did not include “core” intake instruments to be used across all studies to capture key information such as case defining symptoms, the level of illness severity, the illnesses that are considered exclusionary for some case definitions and comorbid for others, and other essential intake information. This may have been addressed in later work by the Baseline group.

Key Recommendations (further details below)

The first four of these would ideally be bundled into one core intake form used across all studies. Some of this information is provided in some of the instruments recommended but haven't been classified. Further, some of these pieces exist in other domains, suggesting further rationalization is needed.

1. "Core" instrument to assess and record the symptom profile, especially for key case defining features
 - a. Recommend implementing DSQ, its scoring method, and additional data elements as an initial core instrument for use across all studies to assess and record the presence or absence of a patient's profile of key symptoms. This will improve consistency and comparability across studies and will also capture other important information such as the age of onset and whether onset was acute or not. (Note: The additional data elements would be used to record whether key case defining criteria (PEM, Sleep impairment, etc) were present or not as e.g. Yes, No, Inconclusive)
 - b. Prioritize the further development and validation of a refined or new core instrument that more fully reflects the patient experience of the disease and addresses any current limitations of the DSQ
2. "Core" instrument to assess illness severity
 - a. If possible, establish an interim core instrument for use across all studies to assess the level of illness severity. If no scale is available, would a simple scale of mild, moderate, severe, and very severe be suitable?
 - b. Prioritize the further development and validation of a severity scale to address any gaps in the interim tool, particularly allowing physical and cognitive severity to be assessed separately.
 - c. This may be intended to come from the QOL domain.
3. "Core" instrument to record key comorbid and exclusionary illnesses
 - a. Recommend a core instrument that specifically records the presence or absence of at least those diseases that are exclusionary for some definitions and/or important confounding illnesses in studies of certain domains. Examples include such as primary sleep disorders, certain primary mental illnesses, or pain syndromes.
4. "Core" instrument to capture other key intake information such as type of illness onset, duration of illness, demographics and other essential information.
5. Rationalize the Baseline recommendations with those provided by other domains where needed. One of the main opportunities appears to be in rationalizing the forms used to record intake information about illnesses and medications.
6. Classify instruments and provide instructions for each
 - a. Designate core, supplementary highly recommended, supplementary, and exploratory classification for each.
 - b. Consider making "Past and Current Illnesses" and "Medications/Other Treatments" core across all studies.
 - c. Provide instructions for all instruments, including who is expected to fill them out. Include accommodations to allow a caregiver to fill out forms if intent is for patient to fill in.
 - d. Provide an NOC for the DePaul Symptom Questionnaire that describes the method, its use and scoring, validation done to date including in other diseases, and its strengths and limitations.
 - e. Recommend the CDC Symptom Inventory be retired because of its deficiencies (Further details below). If it is not

retired, then provide a NOC that lists the method, its use and scoring, validation done to date including in other diseases, and its strengths and limitations. (Further details below)

7. Develop and validate, where needed, instruments for pediatric studies, including an instrument about student attendance and potentially a pediatric instrument for level of illness severity.

Background on Key Recommendations

Current Document	Concern
<p>1. Currently, no instrument has been specified as the one core instrument to assess and record the presence or absence of key case defining features</p>	<ul style="list-style-type: none"> ● Given the intent to allow any case definition, it is essential that there be <i>one core</i> mechanism to assess and record the presence or absence of key case defining criteria. Otherwise, it will be very difficult to compare across studies because each study will have its own interpretation of ME/CFS. ● The current recommendations include the CDC Symptom Inventory and the DePaul Symptom Questionnaire (DSQ) to record the symptom profile of each patient. The CDC Symptom Inventory was designed against Fukuda, is fatigue focused, and lacks certain key features described in the CCC, ME-ICC ● While it has certain limitations, the DSQ has better coverage than the CDC symptom inventory, has been used in a number of studies and by a number of investigators, has been validated including in multiple sclerosis and post-polio, and has been translated into a number of other languages. This tool also captures additional information such as the age of onset and whether onset was sudden or not is not captured

	<p>elsewhere. Finally, a mapping exists from the DSQ instrument to the different case definitions, which would facilitate comparisons across studies using different case definitions.</p> <ul style="list-style-type: none"> • Further research needs to be prioritized as soon as possible to develop and validate a new tool that more broadly reflects the range of symptoms experienced.
2. Currently, no core instrument has been designated to assess illness severity across all studies	<ul style="list-style-type: none"> • ME/CFS covers a wide range of severity, which is an important dimension for sub-setting and/or interpreting studies. The lack of a common method of assessing illness severity across studies will impede cross-study comparisons. • The Quality of Life group has recommended the Bell and Karnofsky Scales and the SF-36 but has not designated any as core for this purpose. The Baseline group has not included any recommendation for such an instrument. • If an instrument is recommended as an interim solution and it does not separately assess physical and cognitive illness severity, then this should be listed as a future need. • Further details are provided below
3. Currently no instrument has been designated as core to capture important comorbid and/or exclusionary illnesses	<ul style="list-style-type: none"> • While the current recommendations include an instrument to capture illnesses, this instrument is not core, which would leave it up to the researcher to decide • The current plan is to allow any definition. Some illnesses are exclusionary for some definitions (e.g. sleep apnea in the CCC) and not for others. At the same time, as the IOM noted, some illnesses may be important confounders in certain studies (for instance, primary sleep disorders in sleep studies or pain syndromes in sleep or pain studies). The IOM also noted challenges in comparing across studies when these differences were not recorded. • This would help facilitate cross-study comparability if at least these specific conditions were recorded across all studies. If the entire “Illness” instrument is not to be defined as core, then an abbreviated core instrument could be created for these conditions. • The alternative might be to have each domain (e.g. pain, sleep, cognition) define instruments for studies focused on those domains but that might be less effective and efficient.
4. The instruments are not classified and for some, no instructions are provided.	<ul style="list-style-type: none"> • Researchers do not have the information needed to decide what instruments to use and how to use them • Some of these topics, e.g. illnesses as above, need core instruments as they can be important confounding factors that need to be considered within studies and in cross-study comparisons. • As above, the CDC symptom inventory lacks important features for the more recent case definitions and should be considered for retirement. (Further details are provided below)

Additional Recommendations, Comments, and Questions

1. Summary: No summary has been provided. Will this be addressed?
2. General Core:

- a. Should this also include a place for the ICD code?
3. Demographic Information (p. 5)
- a. P. 1 – States “This measure is intended for individuals age 18 or over living in the US.” The sentence has an extra “is.” Also, is this saying that this instrument is only intended for U.S. adults? It's unclear why that would be so but if it is, then a pediatric instrument is needed
 - b. P. 1 – The current demographic does not collect age at disease onset and whether disease onset was sudden or not. These are important and would be captured if the DSQ were used. But if the DSQ is not chosen as the core instrument, then these questions will need to be asked somewhere
 - c. P. 1 – Term “CFS” should be updated to “ME/CFS” in heading “Demographic Information – For Baseline CFS”
 - d. P. 1 – why does this repeat ethnicity, which is also listed in the General Core but with more options?
 - e. P. 1 – the item “Do live with them?” is missing the word “you”
 - f. P. 1 – Smoking history needed?
4. Employment (p. 6)
- a. Is the employment education history only for people with ME/CFS? What about the comparator groups? If for both, change the title
 - b. Some terms and concepts apply only to the US populations. Might want to state that.
 - c. If Q#2 is checked, then need direction to skip questions 3 and 4
 - d. Q#5 – needs an option for disabled, applying for disability. Also, is the intent that multiple boxes can be checked? If so, indicate.
 - e. Q#6 – question unclear. Needs rewording
 - f. Q#7 – what if they only ever worked part time?
 - g. Q#8 – first two options are not mutually exclusive. Was the intention that they would be?
 - h. Q#9 – can someone be on more than one? e.g. both SSDI and private disability? If so, add instruction to check all that are applicable
 - i. Q#10 – Patients can sometimes not yet be eligible – e.g. disabled before age 22 with no work history can receive disability once their parent retires or dies
 - j. Q#11 – there can be a primary and secondary reason, at least for SSDI. Should this be clearer. Also
 - k. Q#12 – do you want to know about partial work toward graduate degree?
5. Past and Current Illness (p. 8)
- a. Are all the typical/most important comorbid illnesses included on this list? Are the illnesses that can be easily confounded with ME included on this list? Are the illnesses that are considered exclusionary for ME-ICC, CCC and Fukuda included on this list? Being able to distinguish patients with those will be key to managing confounders and also enabling cross-study comparisons.
 - b. It appears the intention is to list both dx provided by doctors but also some patient reported – e.g. poor appetite. Is that true? Directions at the top of this form would help clarify the intent.
 - c. Has this list been reconciled with recommendations by the neuroendocrine & immunological groups?

- d. Would it help to add a Y/N column for medication currently being taken for any active illness? The actual meds are collected in a concomitant medication CRF
 - e. Should the “Other eye condition” be expanded to be “Other eye condition or visual disturbance” since ME/CFS patients may not have been diagnosed with a specific condition but many have disturbances
 - f. Was it intentional to only ask males about STDs?
 - g. Sleep disorders are listed in both the neurological and the miscellaneous sections – remove from miscellaneous?
 - h. Should OI and POTS also include neurally mediated hypotension
 - i. Add Raynauds to the Cardiovascular section?
6. Family History (p. 14)
- a. The form as laid out is going to be hard to fill in - not much space for listing the disease. Reformat?
 - b. Is there a reason why these specific diseases are listed? And should a space be provided for “other” in each section?
 - c. The term “medically unexplained symptoms” is problematic because part of the literature base uses this term to collect these illnesses plus CFS into a single bucket with a presumed psychogenic cause. Strongly recommend deleting that label and just listing the individual terms
 - d. Add “Other” option for blood disorders
 - e. Cardiovascular should have an option for “Orthostatic Intolerance”, “Raynaud’s”, and “Other”
 - f. Add section for ENT
 - g. Anorexia nervosa and bulimia and in both the Endocrine section and the Psychological. Mistake?
 - h. Rheumatologic should include an option for joint hypermobility syndrome/EDS (type, if known) as well as an option for “Other”
 - i. In Gastrointestinal, IBS should be listed in intestine problems. Should there be an option for “Liver”?
 - j. Should Ehlers Danlos Syndrome be in Rheumatologic instead of other??
7. DePaul Symptom Questionnaire
- a. May need to rationalize parts of the DSQ against other recommended instruments – for instance questions 83, 86 on illness and 84 on medications overlaps with other questions but the other format may be more suitable
8. CDC Symptom Inventory (P. 25)
- a. The form Symptom Checklist – Form A was part of the CDC Symptom Inventory in the CDC multi-site but the label “CDC symptom inventory” appears on page 26. Shouldn’t this label be moved up
 - b. See recommendation above to retire this instrument.
9. Clinical Impressions/Differential Diagnosis (p. 61)
- a. This only asks about differential diagnosis for any abnormal findings. It would be helpful to either give guidance or point researchers to guidance on differential diagnosis for key diseases and for key mental disorders. Is this appropriate for CDEs?
10. Laboratory Test Results (p. 62)
- a. Has this been reconciled with the Immune and neuroendocrine forms for the ones intended for most studies?

- b. Has this form been tested? This asks for the date of earliest, most recent, and most abnormal for a group of tests but the tests in a group may have been tested on different dates. Also, if a given tests results were all in the normal range, should “the most abnormal value” column be filled in for that test or left blank?
 - c. Should this ask whether the result was abnormal or not? Different labs can have different ranges. Recognize this can get complicated as this could be abnormal low or abnormal high.
11. Medications/Other Treatments (p. 66)
- a. Page 1 table, last column – is an “Unknown” choice needed?
 - b. Should medical devices be listed as a choice to keep them from being overlooked?
 - c. Dietary changes needs more space
 - d. Add saline to the list.
 - a. CBT and GET should be removed from the list of “Other Treatments”. First, the terms are used ambiguously and/or differently in other diseases, at times meaning counseling or activity management. Secondly, as studied in this disease, the terms “CBT” and “GET” are used to convince patients they are not sick, only deconditioned and that they should ignore their symptoms and push through it. This is not appropriate treatment and may be harmful.
 - i. If the question is whether the patient has received counseling, then “counseling” would be a better term
 - ii. If the question is whether the patient has used pacing or activity management, then those terms would be better
 - iii. If there is a need to know whether patients received CBT and GET of the form recommended by PACE, that should be asked in a separate question outside of the treatments section. But it’s not clear how that information would be used or why it would be needed as part of a baseline questionnaire

Further Details on the Key Recommendations

1. Rationale for Recommending a Severity Scale

In a review of severity scales, Hardcastle noted the immense variation in presentation and concluded the importance of severity scales for assessing factors such as illness progression and response to treatment (reference below).

The Quality of Life group has referenced some potential instruments, such as the Karnofsky Performance Scale, the Bell Fatigue Scale, and the SF-36 but have not classified them (as core or otherwise) or recommended any other core instrument for this purpose. The Karnofsky Scale has known limitations and the Bell Scale has not been validated.

This will need to be addressed by either the Baseline group or the Quality of Life group. If an interim core instrument can not be recommended for this purpose, then the development and validation of the needed tool should be prioritized.

(Reference -

<http://emerge.org.au/wp-content/uploads/2014/11/Hardcastle-S.-L.-et-al.-Severity-Scales-for-Use-in-Primary-Health-Care-to-Assess-Chronic-Fatigue-SyndromeMyalgic-Encephalomyelitis.-Health-Care-Women-Int-2014-0-1-16.pdf>)

2. Rationale for Recommending DSQ

The DSQ has already been used by the authoring group and others in ME/CFS studies to assess the absence or presence of symptoms, is integrated across domains, assesses frequency and severity, is in multiple languages, has been used in some different diseases (e.g. MS), and has been validated. The DSQ has also been used to map the patients' symptom profiles in a given data set to different case definitions. This would be an important feature as long as different case definitions are being used.

To our knowledge, only two other tools have been used to assess symptoms. One is the CDC Symptom inventory, which has significant limitations as discussed below. The other is the Chronic Fatigue Initiative (CFI) symptom checklist reported in the following paper.

However, to our knowledge, this instrument has not been used in other studies, by other researchers, or in other diseases, and has not been validated.

Reference for CFI symptom checklist

- 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.

3. Rationale to Retire the CDC Symptom Inventory.

The CDC Symptom Inventory was designed for Fukuda. As such, it is fatigue focused, lacks the breadth of symptoms seen in later definitions and in the IOM report, and in some cases, does not accurately convey certain symptoms and isn't adequate for studies that use other definitions.

- a. "Symptom Checklist – Form A" (p. 25 of PDF) focuses on a fatiguing illness. This is not an appropriate way to frame ME/CFS.
- b. The question on PEM frames PEM as fatigue after exertion. This does not accurately reflect PEM as experienced by patients, as described in the IOM, or as in the CDE for PEM. PEM is an exacerbation of all symptoms.
- c. Orthostatic intolerance, a key feature in ME/CFS, is not included in the list of symptoms evaluated.
- d. The Inventory asks about symptoms in the last month. However, Fukuda, the CCC, and the IOM require symptoms in the last six months. For the purposes of a symptom inventory, especially one used to assess the absence or presence of key case defining symptoms, it would seem important to have some consistency in what time frame is used as differences in the timeline could affect which patients are given an ME/CFS diagnosis. This does not preclude the use of different timelines for other purposes such as the assessment of change in symptoms due to PEM, treatment, or illness progression.
- e. The CDC symptom Inventory's questions on key symptoms are very narrow and as a result, may miss the key features of the symptoms. For instance, for PEM, the CDC Symptom Inventory asks about PEM in one way while the DSQ asks in multiple ways as follows:
 - i. CDC Symptom Inventory PEM question:

1. During the past month, have you been unusually fatigued or unwell for at least one day after exerting yourself in any way?
- ii. DSQ PEM related questions
 1. Dead, heavy feeling after starting to exercise
 2. Next day soreness or fatigue after non-strenuous, everyday activities
 3. Mentally tired after the slightest effort
 4. Minimum exercise makes you physically tired
 5. Physically drained or sick after mild activityDSQ also asks the following questions which further probe PEM
 6. If you were to become exhausted after participating in extracurricular activities, sports, or outings with friends, would you recover within an hour or two after the activity ended?
 7. Do you experience a worsening of your fatigue/energy related illness after engaging in minimal physical effort?
 8. Do you experience a worsening of your fatigue/energy related illness after engaging in minimal mental effort? While it needs further refinement, the DSQ does a much better job of reflecting the breadth of the PEM experience. Even aside from the other points listed above, the CDC Symptom Inventory Question is not adequate. The questions for other symptoms are similarly narrow in the CDC Symptom Inventory.

If some researchers use the DSQ and some use the CDC Symptom Inventory to assess the absence or presence of case defining criteria, the comparability of results across studies and across definitions could suffer. And for those researchers using the CDC Symptom Inventory to help identify patients, the accurate selection of patients with ME/CFS could also suffer.

Sleep Domain

Review of Subgroup Materials

Provided by people with ME/CFS

January 31, 2018

General comments

1. Good review of instruments, useful presentation of and good discussion on unmet needs.

Key Recommendations

1. Revise the core *Sleep Questions For All Studies* instrument to:
 - a. Always require DSQ and either remove or make NHANES optional
 - b. Provide a common scoring method and data element to assess and explicitly record the presence or absence of sleep

dysfunction

2. Consider whether instruments never used in ME/CFS, that do not assess unrefreshing sleep, and/or that do not assess both severity and frequency of sleep dysfunction should be classified as anything other than exploratory. If warranted for a specific purpose only, state that purpose.
3. Provide additional guidance and/or references for screening of co-morbid and exclusionary sleep disorders. If needed, revise the *Sleep Focused Study CRF* to capture comorbid sleep disorders regardless of their timing of onset
4. Include additional information about the potential utility of sub-setting sleep study results by other comorbidities such as chronic pain, fibromyalgia and orthostatic intolerance.
5. Clarify recommendations for subsetting by sleep dysfunction and if needed, consider this recommendation in light of cross-domain needs for sub-setting.

Summary of Key Recommendations

Current Document	Concern	Recommendation
1a, 2. The core <i>Sleep Questions for All Studies</i> Instrument allows for either DSQ or NHANES to be used	<ul style="list-style-type: none">● NHANES uses a tool that has not been validated in ME/CFS, does not assess severity as recommended by the IOM, and assesses “unrested during the day” instead of unrefreshing sleep, which the Overview acknowledges is the key feature of sleep dysfunction● This calls into question the validity of this tool as a core instrument for all ME/CFS studies	<ul style="list-style-type: none">● Classify NHANES as exploratory and do not include as part of the Core <i>Sleep Questions for All Studies</i> instrument. If it is part of the core instrument, DSQ should always be required and NHANES optional

<p>1b. The core <i>Sleep Questions for All Studies</i> Instrument does not explicitly capture whether sleep dysfunction is present or not</p>	<ul style="list-style-type: none"> • Sleep dysfunction is a required symptom in IOM and CCC and important in the ME-ICC. But the current core instrument does not include a method to assess and record the presence or absence of sleep dysfunction which will impact cross study comparability and reuse of the data 	<ul style="list-style-type: none"> • Update the core <i>Sleep Questions for All Studies</i> instrument to include a recommended threshold/scoring method for the DSQ questions and a data element to assess and capture the absence or presence of this key symptom
<p>2. Some instruments have been classified as supplemental even though they have never been used in ME/CFS, do not assess unrefreshing sleep, and do not assess both severity and frequency</p>	<ul style="list-style-type: none"> • The IOM stated the importance of assessing both frequency and severity of sleep dysfunction. • The IOM and the Summary reported the importance of unrefreshing sleep as a key feature of sleep dysfunction. • Besides for NHANES, another example is the <i>Sleep Disorder Screening Checklist</i> • Ranking these instruments as supplemental or higher might suggest greater validity than warranted 	<ul style="list-style-type: none"> • Reconsider the classification of the supplementary tools in light of their prior usage in ME/CFS, whether they assess key features like unrefreshing sleep, and whether they assess both frequency and severity. If warranted for a specific purpose– e.g. screening out other disorders – state that purpose.
<p>3. The <i>Sleep Focused Study CRF</i> doesn't provide guidance on assessing co-morbid sleep disorders and doesn't appear to capture comorbid sleep disorders that develop after onset of ME/CFS</p>	<ul style="list-style-type: none"> • Summary Section 6 discusses the need for future studies to use an explicit, systematic way to screen for sleep disorders but no instructions/references are provided for this. • The <i>Sleep Focused Study CRF</i> asks whether there was a history of sleep disorders but this might not account for patients developing comorbid sleep disorders <i>after</i> ME/CFS started. 	<ul style="list-style-type: none"> • Provide initial guidance or references now on screening for primary/comorbid sleep disorders in e.g. the directions for the <i>Sleep Focused Study CRF</i> • If needed, revise the <i>Sleep Focused Study CRF</i> to capture the presence or absence of co-morbid sleep disorders even if onset is after ME/CFS
<p>4. Lacks sufficient guidance on utility of sub-setting by other comorbid conditions beyond sleep disorders.</p>	<ul style="list-style-type: none"> • The IOM report notes differences in sleep studies depending on other comorbid conditions – e.g. POTS, FM. Summary Section 2 mentions FM and autonomic dysfunction but isn't specific on the potential value of sub-setting by these 	<ul style="list-style-type: none"> • Provide additional information to researchers on the potential utility of subsetting by certain comorbid conditions in e.g. the directions for the <i>Sleep Focused Study CRF</i>.
<p>5. Summary Section 6 recommends sub-setting patients in studies and analysis based on whether sleep dysfunction exists or not</p>	<ul style="list-style-type: none"> • It is unclear whether this is intended for: <ul style="list-style-type: none"> – a) ME/CFS sleep dysfunction or b) just comorbid sleep disorders – a) All studies or b) just sleep-specific studies. <p>If this is for ME/CFS sleep dysfunction and all studies:</p>	<ul style="list-style-type: none"> • Clarify the recommendation in Summary Section 6.

	<ul style="list-style-type: none"> • This may be challenging, given the broader cross-domain needs for sub-setting by e.g. duration of illness, type of onset, severity, presence or absence of other hallmark symptoms like PEM, etc. 	<ul style="list-style-type: none"> • A cross-domain recommendation for a sub-setting strategy may be needed to accommodate the broader range of needs for sub-setting
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Miscellaneous Comments

1. Purpose of each instruments: Section 1 of the Overview appears to list a number of different purposes of the instruments – e.g. a) general assessment b) screen for other sleep issues c) assess impact of sleep on function d) instruments to assess unrefreshing sleep. Has such a list been agreed upon? It would be helpful if the table in Section 3 listed the intended purpose of each instrument. Also, does this list include comparison to other sleep disorders or assessment of change in sleep following treatment or exertion? If not, should those be on the list?
2. Additional research needs: The IOM report notes that sleep impairment may change over the course of the illness. The IOM also notes the need to use ill controls. Should these be added into Summary Section 6? Also, some of the discussion points in Section , such as the discussion on medication, might be useful to add to the CRF instructions.
3. Timescale of evaluation: At least one instrument (DSQ) asks for evaluation of sleep symptoms for the last six months, at least one (Pittsburgh Sleep Quality Index) over the last month, and at least two (Sleep Disorders Screening Checklist, NHANES) do not specify a timeframe. Do these differences reflect differences in the intended purpose of each instrument (e.g. assessing treatment response time frame likely different than a general assessment)? Has the group evaluated the impact of timeframe on the ability to compare across studies, depending on the purpose of the instrument?
4. Ceiling and floor effects: What is known about any ceiling and floor effects of these instruments? Could that be explicitly listed in the NOC for each instrument?
5. Other comments:
 - a. The link for the “Sleep Assessment Questionnaire – Moldofsky” instrument goes to his paper, not the tool itself or the website about the tool.
 - b. Section 2 of the Overview includes a sentence that starts “I think” – recommend “we.”
 - c. The Stanford Sleepiness Scale states a limitation of “Very brief and easy to administer throughout the day.” Does not appear to be a limitation.

Additional Background on Key Recommendations

1. Use of NHANES

- a. The IOM and the Overview highlighted the importance of unrefreshing sleep. But according to one of the papers (Zhang et al 2013) referenced in the *Sleep Questions For All Studies CRF*, NHANES doesn’t ask about unrefreshing sleep, it asks about “unrested during the day.” The paper acknowledges this as a limitation, stating “the validity and reliability of the measure of NRS [nonrestorative

sleep] in the current study has not been established” and that NRS “referred to ‘feeling unrested’ during the day rather than specifically targeting this symptom upon awakening”

- b. NHANES also does not assess sleep reversal and has not been used in ME/CFS, does not assess *severity* of sleep dysfunction as recommended by the IOM.

Biomarker Domain

*Review of Subgroup Materials
Provided by people with ME/CFS
January 31, 2018*

General comments

1. Recognizes the importance of this domain for the field, the need to move beyond symptom-only definitions, and the need for replication of prior findings from small studies in larger cohorts.
2. Particularly well researched and exhaustively referenced, providing specific guidelines with references for protocol & data reporting in each biomarker subdomain.
3. Acknowledges the importance of and unique issues related to cohort composition and in these studies, encouraging at least full transparency in diagnostic criteria utilized for study inclusion, attention to achieving study size needed for power calculations, inclusion of pediatric, male, genetically diverse and severely ill populations, and the need for appropriate control populations depending on the nature of the study.
4. Appropriately identifies many ethical issues specific to ME/CFS such as patient burden in commuting to study site especially during longitudinal studies, risks of invasive sample collection and difficulty of inclusion of severely ill in studies.
5. Acknowledges the need for consideration and reporting of confounding factors, but does not sufficiently address these or provide researcher education/guidelines around accounting for confounders in the design and interpretation of ME/CFS studies.
6. Entirely omits discussion of the need to correlate objective measures with patient-reported symptoms, disease severity or subgroup composition. Includes no review of instrumentation capture patient symptom status/severity, and issues no guidelines to researchers on use of symptom instrumentation in study analysis.

Key Recommendations

1. Expand upon efforts to identify and educate researchers on confounders unique to ME/CFS.
2. Update recommendations to include researcher education on the need to perform correlative analysis of objective findings with patient-report symptoms, disease severity and duration. Review and supply instrumentation recommendations for capturing symptoms and severity, and encourage analyses which identify subgroups or linkage to symptoms.

Summary of Key Recommendations

Current Document	Concern	Recommendation

<p>Confounding factors</p>	<p>Guidelines do not include an exhaustive list of confounders to be anticipated by researchers, nor do they include recommendations for mitigating these influences.</p>	<p>Given the uniqueness of ME/CFS, it is warranted that the subgroup expand these recommendations in great detail. (See below for further discussion.)</p>
<p>Patient symptoms</p>	<p>No review of instrumentation to collect patient symptom data was conducted. No recommendations for correlation of objective measures with symptom profile, disease duration or severity are provided.</p>	<p>Encourage protocols which perform correlation analysis of objectively measured variables with patient symptoms, disease duration and disease severity. Review and recommend instrumentation to support comprehensive collection of these patient-reported data to enable such analyses. Encourage subgroup analysis.</p>
<p>Cohort reporting</p>	<p>Recommendations on cohort composition reporting are not specific enough. Instrumentation is not reviewed/recommended which would enable sufficient reporting.</p>	<p>Delineate exactly which elements of cohort composition must be reported (i.e. case-defining criteria for inclusion, exclusionary criteria and comorbidities, disease duration, objective severity measures such as Karnofsky score, sex/racial composition). Provide recommendations on avoiding bias in cohort selection, especially for genetic analyses.</p>
<p>Medication Questionnaire</p>	<p>Omits survey of supplement intakes</p>	<p>Include on survey supplement intakes, which many ME/CFS patients utilize abundantly. (See below for further discussion.)</p>

Defers to the IRB in considering issues related to more invasive techniques than currently proposed	Given the general unfamiliarity of the nature of ME/CFS, the IRB may not be best suited to account for these issues.	It is encouraged that the subgroup continue to play a role in this process to ensure potential harms are mitigated.
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Additional Comments

Confounders

The subgroup has not accounted for the influence of the fluctuating nature of the disease on study sampling. A patient’s relative status at time of sample collection (good day/bad day) will likely have a profound impact on the biometrics being measured, and attempts to capture patients at their worst would likely improve signal:noise in objective measures. However no instrumentation has been reviewed or recommended to capture patients’ symptom status, nor guidelines for researchers in accounting for such influences in study design and instrumentation use. Comorbid conditions is another example of a key confounder not being accounted for can have profound impacts on the dataset. At a minimum, a thorough list of such considerations specific to ME/CFS should be supplied to researchers. Ideally, detailed recommendations for proposed methods to limit confounder influence should be generated by the subgroup and any missing instrumentation developed and deployed.

Patient Symptom Data

The subgroup has exhaustively identified a suite of objective measures for study in ME/CFS and has provided thorough recommendations for the detailed reporting of these findings. However, no attempt has been made to ensure tools are provided for researchers to appropriately link these findings to patient-reported metrics such as symptoms, disease severity, or disease duration. The Institute of Medicine Report noted the importance of correlating subjective reports of symptoms with objective measures. In the absence of an in-depth understanding of the etiology and pathophysiology of ME/CFS and identification of an objectively measurable driving factor, reliance on the patient-reported disease experience is an inevitably critical element of studies which aim to understand the disease pathophysiology and define objective biomarkers. Until objective measures are validated and biomarkers identified, patient-reported symptoms are all we have to rely upon to assess any given variable’s linkage to the disease experience. ***The subgroup’s lack of review and include instrumentation which might capture these essential data could reflect a significant oversight in the approach to biomarker identification.*** A recent preliminary study tightly associating biologic variables with daily symptom fluctuations (<https://youtu.be/QHlvcw9SNFo>) demonstrates the power of a frequently administered instrument in leveraging patients’ assessment of their physical experience to

inform interpretation of subthreshold biometric measures, illustrating the potential of this type of tool in biomarker identification and subgroup identification. Instrumentation to capture patient-reported disease experience is thus a vital element of biomarker studies and should be thoroughly reviewed by the subgroup with recommendations for capturing at least a basic measure of this data element in all biomarker investigations. ***Encouragement and guidance should be supplied within the CDE recommendations on the importance of performing correlative analysis of patient-reported symptoms with objective measures, and standards for reporting such analyses should be articulated in the recommendations. Additionally, encouragement and guidance should be supplied to researchers in performing subgroup analyses across a variety of metrics (i.e. case definition, symptom groupings, duration, severity, etc.) within the datasets generated.***

Medication Questionnaire

Reporting of medications *AND/OR SUPPLEMENT* (i.e. OTC herbal/mineral/nutritional supplements, probiotics, IV fluids) intakes and any changes to intake prior to study visit/sample collection is of relevant concern for biomarker studies. Intake of supplements may profoundly impact the proposed variables to be measured, therefore an accurate assessment of these potential influences prior to assessment is strongly warranted. For example, a patient may take a daily curcumin supplement (potent transcriptional modulator) prior to a blood draw, thereby impacting gene expression results; or a daily berberine/querctetin supplement (potent mTOR inhibitors/translation modifiers), thereby impacting proteomic results; or daily probiotics or antiviral supplements, thereby impacting microbiome results. As use of such alternative therapies is highly prevalent among ME/CFS patients, all study designs and patient communications should account for such potential behaviors and influences, capturing all intakes and providing clear instructions and explanations of those to be abstained. Wording of documentation should include verbiage encouraging patients to report all supportive interventions and anticipatory behaviors, not just prescription medications.

Inclusion of Severely Ill

The subgroup has recognized the limitations of including severely ill in biomarker studies, but has not discussed the potential for patient-submitted genetic data (supplied from commercial services) or mail-in saliva sampling.

Pain Domain

*Review of Subgroup Materials
Provided by people with ME/CFS
January 31, 2018*

General comments

1. Good descriptions of the instruments and discussion of ME/CFS pain research confounders as a result of comorbid pain conditions.

Key Recommendations

1. Adopt a core instrument to assess and record the presence or absence of pain as a case defining criterion
- Note: a cross-domain instrument that assesses all key symptoms could address this requirement
2. Consider providing a CRF for *Pain Focused Studies* that records co-morbid pain disorders such as FM and if needed, information on medication use or other factors that could confound interpretation of results.
3. Consider providing guidance on important considerations for pain-focused studies. Examples could include what should be tracked (e.g. pain location, type of pain, impact on function, severity of pain) and considerations in managing confounding factors such as the impact of exertion, medication, comorbidities, etc
4. Consider reassessing whether instruments only previously used in FM should be classified as supplemental highly recommended or supplemental, given that the IOM reported different results when comorbid FM was present.
5. Revise the Summary table to include the location, the type of pain (e.g. migratory, radiating), and the specific purpose of each instrument (e.g. assess level of pain, impact on function, change in pain as result of exertion or treatment, etc)

Background on Key Recommendations

Current Document	Concern
No core instrument has been provided to assess presence or absence of pain as a case defining criteria	<ul style="list-style-type: none"> ● Pain required for the Canadian Consensus Criteria and mentioned in all the others ● The IOM notes that the ability to make comparisons across pain studies is limited by the lack of a common case definition. Given that any case definition can be used, it will be important to assess and record whether pain is present or not. This will facilitate comparisons across studies. ● The DSQ pain questions could be used for this purpose as DSQ has been used in ME/CFS, assesses both frequency and severity as recommended by the IOM, and has a scoring method for the tool.
No CRF or guidance for pain focused studies	<ul style="list-style-type: none"> ● The IOM notes the impact of comorbid pain conditions on the findings in studies supporting the need to consider these in studies. The IOM also noted the impact of PEM on pain suggesting the need to manage the impact of unplanned exertion. Presumably, studies will also need to consider/manage the impact of pain meds ● The CRF for Sleep Focused Studies and the Guidance for PEM Focused Studies may provide useful models

Autonomic Domain

Review of Subgroup Materials

Provided by people with ME/CFS

January 31, 2018

General comments

1. We appreciate that the thought process behind the committee's recommendations reflects a deep understanding of the autonomic dysfunctions common in ME/CFS and the confounding factors in assessing them.
2. While most of the key considerations were addressed, or at least acknowledged, somewhere in the report, it lacks an overarching, comprehensive, or cohesive set of explanations and guidelines.
3. The committee is applauded for taking the initiative to adapt an existing instrument to better reflect and account for the symptoms of people with ME/CFS. We hope this instrument will be appropriately refined and validated in a timely manner.

Key Recommendations

1. Provide guidance for researchers, particularly those new to ME/CFS.
 - a. Summarize best practices for conducting autonomic studies to consider, address, and/or mitigate the unique symptoms and limitations in ME/CFS, such as post-exertional malaise (PEM). Reports from both the Neurological and PEM domains might be used as models of good guidance.
 - b. Provide guidance regarding staying on medication/supplements for all autonomic research, not just for the Passive Standing Test.
 - c. Provide basic information about each of the instruments listed in the report, including those that are not recommended. Particularly since DSQ is likely to be used already, having been recommended by several subgroups, researchers should know why they should also use at least one separate autonomic instrument.
 - d. Include further explanation and relevant supporting references for the focus on assessment of OI symptoms in ME/CFS.
2. Verify that the Baseline Domain's Core instruments on patient and family medical history ensure data collection specifically on all diseases and conditions relevant to autonomic dysfunction.
3. Recommend a patient-reported instrument that assesses abnormal heart rate, arrhythmias, palpitations, and other autonomic cardiac symptoms.
4. Provide information and supporting references on why, when, and how to use the Beighton Score, and the relationship between hypermobility (in patient or family history) and autonomic dysfunction.
5. Provide clarity for researchers and patients whenever the terms "stand" or "sit" (or their grammatical derivatives) are used. Consider when and how sitting upright can be a proxy for standing.

- 6. Include a specific line in the general instructions indicating that the Modified Orthostatic Symptom Grading Scale has not been validated. Include a strong statement in the “Unmet Needs” section recommending validation of the Modified Orthostatic Symptom Grading Scale.
- 7. Refine problematic questions in the Modified Orthostatic Symptom Grading Scale.

Description of Key Recommendations

Current Document	Concern	Recommendation
<p>1a. Lacks guidance for researchers new to ME/CFS doing autonomic focused studies</p>	<ul style="list-style-type: none"> ● Researchers, particularly those who are new to the ME/CFS field, are unlikely to be aware of or appreciate the unique aspects of the disease including <ul style="list-style-type: none"> ○ the confounding factors that may affect assessment of autonomic dysfunction ○ the physical or cognitive needs and limitations of patients ○ the potential for short- or long-term harm caused by exertion (post-exertional malaise) ○ the variability of symptoms over time (hours, days, weeks, and months) 	<ul style="list-style-type: none"> ● Include a guidance document summarizing best practices for doing autonomic studies, addressing issues specific to people with ME/CFS including: <ul style="list-style-type: none"> ○ Risks of PEM due to any form of exertion and ways to mitigate these risks. ○ How PEM from travel or other activities may affect study results¹ ○ The potential challenge and danger of even ‘passive’ standing for people with severe ME/CFS. ○ How to decrease patient burden and risk to patients due to exertion by identifying the type of data of greatest importance to collect for study ○ Description of common comorbidities that may affect autonomic studies and guidances on how to handle these (e.g., consider need for subgrouping).

¹ We propose that it may be worth documenting and considering where a subject is on the day(s) of testing with respect to his/her recent baseline (last 3-6 months).

		<ul style="list-style-type: none"> ○ Recommendation that subjective symptom data should always be collected alongside objective instruments, and correlations be analyzed. <p><i>Note:</i> The Neurological and PEM domain reports provide good models for such guidance.</p>
1b. Lacks general guidance for medication continuation/use before or during the studies	<ul style="list-style-type: none"> ● Medications and supplements can have a profound effect on the results obtained, and must be taken into consideration both before and during the testing. ● Some patients cannot safely discontinue medications in order to participate in research studies. Concerns about skewing results by excluding such patients must be weighed with concerns about the confounding factors of medication use and concerns about requesting short- or long-term discontinuation of medication. ● If medications/supplements are to be discontinued, guidelines should be included on identifying which medications/supplements are of greatest concern for autonomic studies and determining how long in advance they must be discontinued. ● Researchers may not know how to approach these issues, particularly in the context of ME/CFS 	<ul style="list-style-type: none"> ● Include guidance around medication/supplement usage in general. (Some guidelines are noted in the section on administering the passive standing test, but overall guidelines for all autonomic studies should be enumerated). Guidance should help researchers determine how to address medication usage in their research subjects, by including complete information on how to <ul style="list-style-type: none"> ○ weigh patient safety and well-being vs. the importance of clean, relevant data from an appropriately representative cohort ○ determine which medications/supplements are likely to have an effect on the particular study ○ determine how long in advance of the study a medication/supplement should be discontinued
1c. Lacks clear explanations for instrument recommendations	<ul style="list-style-type: none"> ● The list of instruments that had been reviewed lacks sufficient information about each instrument. I.e., what they assess, what they have been used for, whether they have been validated, etc. ● There is little information on the reasons why those that are not recommended are inadequate. Many researchers may have preferences or biases for or against specific instruments or will already be using some other instruments (e.g., the DSQ), so 	<ul style="list-style-type: none"> ● Each recommended instrument should have “Notice of copyright” that includes: <ul style="list-style-type: none"> ○ description ○ scoring method ○ references, and/or origin and previously accepted use(s) ○ any known psychometric properties ○ a link to the tool

	<p>systematically laying out the reasons for the recommendations (and exclusions) supports the goal of promoting a more standardized approach to data elements in ME/CFS.</p>	<ul style="list-style-type: none"> ○ reason for recommendation for/against use in ME/CFS autonomic studies ○ instructions for the Case Report Forms ● A brief description and explanation of those instruments that are not recommended should also be included.
<p>1d. Lacks clear explanation for focus on OI over other autonomic symptoms</p>	<ul style="list-style-type: none"> ● The report does not provide a clear explanation for the reasoning behind the greater focus on OI over other autonomic symptoms in ME/CFS. 	<ul style="list-style-type: none"> ● Include further explanation and relevant references for the greater focus on assessment of OI symptoms, over other autonomic symptoms, in autonomic studies of ME/CFS. If other aspects of autonomic impairment are also important, then additional instrumentation may be required. If so, this should be explicitly discussed in the summary report.
<p>2. Does not ensure that relevant patient and family medical history are collected</p>	<ul style="list-style-type: none"> ● This report assumes a level of cross-domain coordination that is not evident and may not occur. ● It appears that the Baseline Domain does not list as ‘Core’ any instruments that record information about several illnesses or diagnoses relevant to autonomic symptoms or dysfunction, either in the patient or family medical histories. 	<ul style="list-style-type: none"> ● Verify that the Baseline Domain’s core instruments collect information about the patient and their family medical history relating to all the diseases and conditions relevant to autonomic dysfunction, including EDS, POTS, neurally mediated hypotension, forms of syncope, Raynaud’s, and a space for “Other” (with a blank for patient input).
<p>3. Does not recommend any patient-reported assessment of heart rate, arrhythmias, palpitations, etc.</p>	<ul style="list-style-type: none"> ● Elevated heart rate, arrhythmias, and palpitations are common symptoms of autonomic dysfunction, including OI, yet none of the recommended CRFs capture much information about these symptoms. ● The Passive Standing Test does record heart rate, but it is only a 1-day snapshot. Since symptoms can vary dramatically from day-to-day (or even hour-to-hour) in people with ME/CFS, and can be affected by travel or other activities, this may not be a good indication of the overall patient experience. 	<ul style="list-style-type: none"> ● Recommend a CRF that asks questions about heart rate, arrhythmias, palpitations, and other autonomic cardiac symptoms <p>OR</p> <ul style="list-style-type: none"> ● Include questions about heart rate, arrhythmias, palpitations, and other heart-related autonomic symptoms in the Modified Orthostatic Symptom Grading Scale

<p>4. Lacks information on why or how to use the Beighton Score</p>	<ul style="list-style-type: none"> ● Many researchers, including those who are new to the ME/CFS field, are unlikely to be aware of or appreciate the connection between hypermobility, ME/CFS, and autonomic dysfunction. ● Is it unclear when and how the Beighton Score should be used or taken into consideration. 	<ul style="list-style-type: none"> ● Include relevant references on the relationship between hypermobility, ME/CFS, and autonomic dysfunction. ● Include information on when and how to use the Beighton Score (not just how to administer the test and obtain a score).
<p>5. Lacks clear guidance around standing and sitting</p>	<ul style="list-style-type: none"> ● It is unclear when sitting upright might serve as a proxy for “standing” for severely ill ME/CFS patients ● It is unclear whether and when the sitting position itself must be specified or considered (with feet propped up <i>vs.</i> feet dangling or on the ground, head and upper back supported <i>vs.</i> held upright by one’s own strength, <i>etc.</i>). 	<ul style="list-style-type: none"> ● Provide clarity for researchers and patients whenever the terms “stand” or “sit” (or their grammatical derivatives) are used. Consider when and how sitting upright can be a proxy for standing. ● Provide clarity for researchers on how to take into consideration that fatigue and other symptoms can be caused by the effort of standing or sitting upright by one’s own strength in people with ME/CFS, separate from autonomic dysfunction. (This is acknowledged in a general way, but not always fully addressed in the report or Modified Orthostatic Symptom Grading Scale.)
<p>6. Recommends an instrument (the Modified Orthostatic Symptom Grading Scale) that has not been validated</p>	<ul style="list-style-type: none"> ● While we agree with the committee’s conclusion that existing instruments do not adequately assess OI derived from autonomic dysfunction, due to the unique confounding factors in ME/CFS, the proposed modifications to the Orthostatic Symptom Grading Scale are extensive and unvalidated. 	<ul style="list-style-type: none"> ● It must be made clear that the Modified Orthostatic Symptom Grading Scale has not been validated. A specific line should be included in the general instructions indicating that this instrument has neither been validated nor used previously in ME/CFS. ● Include a strong statement recommending validation of this new instrument, perhaps through a specific NIH RFA. ● Information should be included indicating <ul style="list-style-type: none"> ○ when and how the original Orthostatic Symptom Grading Scale has been used ○ how much modification has been made ○ why these modifications were made

		<ul style="list-style-type: none"> ○ how the Modified Scale should be interpreted, suggested thresholds, <i>etc.</i>
7. Some questions on the Modified Orthostatic Symptom Grading Scale are problematic	<ul style="list-style-type: none"> ● Some of the questions in the Modified Orthostatic Symptom Grading Scale may be hard to understand or respond to accurately. 	<ul style="list-style-type: none"> ● See suggestions below (#1 in Additional Information on Key Recommendations)

Additional Comments

1. Include all recommended CRFs within the report itself. The COMPASS-31 questionnaire currently requires a researcher to request it from a particular researcher, which poses barriers to access. The exclusion of the COMPASS-31 instrument from the report also leads to questions about what part of the COMPASS-31 is being recommended for usage - is it only Supplemental Appendix 2, or are there other parts, as well?
2. Consider including a swallow test to test that aspect of autonomic function.
3. Questions/comments regarding the Passive Standing Test:
 - a. The final column in the data collection table has space for patient feedback on symptoms over the course of the test, but no information is provided on eliciting useful data on this from subjects. Consider offering subjects a visual scale of each symptom that they can point to.
 - b. For some patients talking while supine can increase their heart rate considerably. Consider recommending that subjects avoid talking and all other forms of exertion during initial supine stage.
 - c. Is 2 minutes long enough to recover to baseline? Clarify what researchers might expect to learn in these 2 min of recovery.
4. Researchers should be warned that they should plan to provide ample rest time after *any* form of exertion (physical, mental, emotional).

Additional Information on Key Recommendations

1. Modified Orthostatic Symptom Grading Scale:
 - Clarify the term “stand up” a bit more. It is not completely clear that the activity being discussed is about the transition from lying down to standing or whether it is about standing for some duration. Furthermore, can sitting upright serve as a proxy for standing?
 - Refine questions to address the following:
 - Q2, 7 and 12: How would a patient respond if she/he needs to lie down, rather than merely sit down, to achieve relief? What if the patient has these symptoms upon transitioning from lying down to sitting upright?
 - Q3: The inclusion of the word “exertion” means that fatigue from causes other than autonomic likely will be reflected in the answers to this question.

- Q5 and 15: In questions about duration of standing, it is difficult to effectively separate the symptom exacerbation due to autonomic problems from PEM. (Though, we acknowledge that this distinction is generally challenging to make in ME/CFS.)
- Q3, 4, 8, 9, 10, 13 and 14: When discussing a symptom's interference with activities, it is hard to distinguish which of the autonomic symptoms is the cause of the interference - if a patient has both fatigue and lightheadedness, which of them is interfering with standing may be difficult to assess. It is also hard to differentiate autonomic dysfunction (or symptoms thereof - fatigue, lightheadedness, and cognitive dysfunction, respectively) from the same or similar symptoms due to other causes.
- Q4 and Q9:
 - It is unclear how a subject would determine whether their symptoms are mild, moderate, or severe - more guidance is necessary.
 - Interference in work/school is on a very different level from bathing/dressing, with chores being somewhere in between, so it is confusing to lump them all together. This may be combined with the previous point to arrive at a clearer set of possible responses. For example:
 1. "Fatigue *mildly* interferes with activities of daily living (e.g., school, work, but not chores, dressing or bathing)"
 2. "Fatigue *moderately* interferes with activities of daily living (e.g., school, work, and chores, but not dressing or bathing)"
 - How is answer #3 functionally different from #4? Both state "severe" interference, but #4 requires bed/wheelchair-bound, which is presumably more severe than #3. Since the descriptor is the same ("severe"), anyone who isn't bed/wheelchair-bound would be disinclined to claim "severe" interference, even if they felt it was worse than "moderate".
- Q6-10:
 - What is the difference, if any, between lightheadedness and dizziness? The use of just "lightheadedness" seems to expect patients to distinguish between them.
- Q11-15 (on Cognition): It is hard to know what "thinking or concentrating" means, without examples of what kinds of thinking are at issue (carrying on a conversation? doing math problems? reading? *etc.*).
- Q16-20 (on blurry vision): Would seeing stars or splotches upon standing up be similar to or count as "blurry vision"? The use of just the term "blurry vision" seems to separate it from other similar symptoms.
- Q18: What if blurry vision occurs occasionally, but is not related directly to standing? Does this differentiate the trigger as autonomic vs. another cause? E.g., What if cognitive effort causes blurred vision?

[...]

Hi,

Please find enclosed comments for the ME/CFS CDE public review. These comments relate to the Post-Exertional Malaise Subgroup.

These comments come from a working group from our patient forum (Science For ME <https://www.s4me.info>) who have analyzed PEM questionnaires and produced a series of recommendations. As part of this work we did a survey of over 700 patients to support the analysis and have included an additional appendix with the results.

I'm including the main text of the analysis below and in addition attaching a word document containing the analysis and an additional appendix in the form of a pdf containing the survey results.

Please contact me if there are any questions.

Thanks



Science For ME

<https://www.s4me.info>

Submitted Analysis

Submission to the public review on Common Data Elements for ME/CFS: Problems with the proposed measure of post-exertional malaise



This submission has been prepared by ME/CFS patients with an interest in research, including some who have published in peer-reviewed journals in relation to the disease. We are grateful to the NIH/CDC for the opportunity to comment on its plans.

Summary: Post-exertional malaise (PEM) is the cardinal symptom of ME/CFS. The accurate identification of PEM therefore underpins good ME/CFS research, especially that which is aimed at discovering the biology behind the disease. The NIH/CDC PEM Subgroup has recommended using the PEM subscale of the DePaul Symptom Questionnaire (DSQ) as the primary basis of a core common data element (CDE) to identify PEM in all of the studies that they fund from now on. This subscale has many desirable qualities, but we have concerns about its selection as it was not developed as a standalone, PEM-specific scale. In particular, there is a mismatch between the DSQ PEM subscale and the Subgroup's own definition of PEM. Also, there are questions about what the DSQ PEM subscale actually measures, both from research evidence and our poll, which found that two thirds of more than 750 patients said that the DSQ subscale description of PEM did not broadly reflect their own experience. We believe that the Subgroup's primary recommendation should be that the NIH/CDC fund the urgent development of a new, validated scale designed specifically to ascertain PEM, developed in partnership with patients. We discuss a potential interim strategy while such a scale is being created.

Post-exertional malaise (PEM) is widely regarded as a key symptom in ME/CFS. The Common Data Elements (CDE) PEM Subgroup note that the Institute of Medicine (IOM)¹ criteria for the disease, as well as the Canadian Consensus criteria and the International Consensus criteria, all agree that PEM is required for an ME/CFS diagnosis. The Subgroup states that all research studies should use a consistent tool to ascertain the presence of PEM in research participants, to ensure that studies are compatible.

The PEM Subgroup noted that there were few well-tested questionnaires designed to ascertain PEM but that the PEM subscale of the DePaul Symptom Questionnaire (DSQ)² had been tested, including independently (Murdock et al., 2016), used in several ME/CFS studies, and evaluated in several diseases (NINDS/CDC, 2017, p. 2). Test-retest reliability and internal consistency are both good. The Subgroup therefore chose the subscale as the basis of the core CDE instrument for ascertaining PEM in all ME/CFS studies.

The PEM subscale was developed by Professor Leonard Jason³ and colleagues as just one part of the much larger DSQ, which was designed to capture a wide range of ME/CFS symptoms. The DSQ has been shown to be effective in separating ME/CFS patients from both healthy and sick controls, and has good measurement properties, including high test-retest reliability. It has been widely used as a diagnostic tool. A recent preliminary study has shown that it detected 92% of true cases and 75% of negative cases, compared with the benchmark of physician assessment of patients (Strand et al., 2016). Jason recommends the scale to be used as a preliminary screening, prior to physician assessment.

¹ The Institute of Medicine has now been renamed the National Academy of Medicine but we use the former name in this document because patients are familiar with 'the IOM report'.

² The PEM section of the full DSQ can be seen on p. 9 of NINDS/CDC, 2017.

³ We are grateful to [redacted] for his comments on earlier versions of this paper. Although he is not in full agreement with our perspective, his insights have been very valuable.

Furthermore, Jason's work has helped inform and move forward discussions on a single, agreed case-definition — something that exists in most diseases, but is a critical and as yet unmet need for ME/CFS.

Our comments in this submission to the PEM Subgroup are solely about the DSQ PEM subscale that the Subgroup recommends to identify post-exertional malaise, and not about the wider use of the entire DSQ, whose importance we recognise.

The DSQ PEM subscale, being one part of a major scale, has, understandably, not received as much attention to its validation as the whole. This raises the question of whether it is fully suitable for identifying PEM cases, as the Subgroup hopes. We present the issues below, including concerns about the overall method of PEM assessment proposed by the Subgroup.⁴

1. Substantial mismatch between the 'IOM' and DSQ PEM scale descriptions of PEM

The PEM Subgroup state (NINDS/CDC, 2017, p. 7) that, for the PEM CDE, they are adopting a definition of PEM based on those in the IOM, CCC and ICC case criteria (for brevity, the 'IOM definition'). They summarise the definition as follows:

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 such as toileting, bathing, dressing, communicating, and reading can trigger PEM.

The IOM, CCC and ICC case definitions of ME/CFS have been generally well received by patients. However, these PEM items are very different to the five symptoms that form the DSQ PEM scale:

1. Dead, heavy feeling after starting to exercise.
2. Next day soreness or fatigue after non-strenuous, everyday activities.
3. Mentally tired after the slightest effort.
4. Minimum exercise makes you physically tired.
5. Physically drained or sick after mild activity.

The DSQ PEM items focus largely on feeling fatigue or tiredness, and, apart from one item, do not mention that post-exertional symptoms may be delayed. There is no mention of prolonged recovery or the loss of functional capacity. The IOM list, in contrast, does mention these additional aspects as well as a considerably greater range of symptoms, including flu-like symptoms and others that indicate immune symptomology. The references in the DSQ PEM items to 'exercise' may suggest to patients a high threshold for some symptoms. The IOM descriptors, in contrast, make it clear that the trigger for PEM is 'minimal amounts of... exertion' that can include even basic activities of daily living such as toileting or reading. They are also clear that cognitive as well as physical exertion can be a trigger.

⁴ Note that we restrict ourselves in this submission to discussing an instrument to determine PEM caseness, not one to measure the extent of PEM.

These differences raise concerns that DSQ PEM scale – especially individual items on it – may not be a good fit for PEM. But in fact, although our current focus is on the suitability of the DSQ PEM scale for case ascertainment, neither that scale nor the IOM descriptors have been validated on PEM cases identified by clinicians. Whatever questionnaire is to be used to ascertain PEM will need such validation.

2. Determination of caseness on the basis of a single question

A further cause for concern with using the DSQ PEM scale as an ascertainment tool is that it only takes a single symptom to be present at moderate severity and for more than half the time for a patient to be considered a PEM case. However, the IOM description of PEM indicates a multifaceted complex of symptoms and it is unclear whether a single symptom could be a sound basis for ascertaining PEM. Also, considering that some of the symptoms listed are quite unlike those on the IOM list, a patient could be diagnosed with PEM on the basis of a symptom that may not reflect PEM. Again, this is a matter for validation and for designing a scale specifically for case ascertainment.

3. DSQ PEM items may describe other ME/CFS symptoms

Individual DSQ PEM symptoms are very common among patients, even in studies that do not use the DSQ as a mandatory screen for PEM (Klimas et al., 2015, McManimen, Sunnquist & Jason, 2016).

However, this does not necessarily mean that the scale measures PEM. For example, Items 3 and 4 ('Mentally tired after the slightest effort' and 'Minimum exercise makes you physically tired') may simply reflect exertion intolerance, another key symptom of ME/CFS.

Further evidence that the DSQ PEM scale might not fully capture PEM comes from a survey by McManimen, Sunnquist, and Jason (2016). They found that post-exertional symptom descriptors from the DSQ PEM scale and other sources, including the International Consensus Criteria, resolved into two factors. The first and largest describes a general exacerbation of the symptom complex and included three of the five DSQ PEM items, but these were the weakest-loading items on that factor, suggesting that other descriptors capture PEM more precisely. For example, the highest-loading item was simply 'post-exertional malaise'. The two other items of the DSQ PEM scale loaded on the second and smaller factor, 'muscle fatigue', which is perhaps a less obvious fit for PEM. Professor Jason reported that this study, and other recent work from his group, has led them to develop a new version of the DSQ PEM scale that incorporates additional questions (Jason, 2018).

The PEM subscale does appear to distinguish between ME/CFS cases and healthy controls: Jason et al. (2015) found that a PEM factor primarily made up of the five subscale items identified patients and controls with over 90% accuracy. Murdock et al. (2016) also found that the DSQ PEM subscale, with the addition of items on fatigue and sleep, differentiated between ME/CFS patients and healthy controls (OR 1.23, $p < .001$). However, it is unclear whether the ability to discriminate between ME/CFS cases and others was on the basis of PEM itself, rather than other ME/CFS symptoms identified by the subscale.

Despite our concerns, the DSQ PEM scale might, in fact, be accurately ascertaining PEM. But, taken together, these various studies emphasise the importance of validating any PEM scale against some external indicator of PEM. In the current absence of objective biological measures, this would be the patient's or an expert clinician's judgement that the patient has PEM. The DSQ PEM scale has not been validated in this way, which is not surprising given that it was not developed as a standalone scale. It is important that the DSQ PEM scale, and any other scale developed to ascertain PEM, are validated in terms of their accuracy in identifying both cases and non-cases.

Such validation is crucial, given that accurate determination of PEM will underpin all research into ME/CFS. And, as the Subgroup notes, it will be important to validate any scale by using comparison groups consisting not just of healthy people but of those with other diseases.

4. DSQ PEM items indicate high levels of PEM in multiple sclerosis patients

Results from applying the DSQ PEM scale to multiple sclerosis (MS) patients also give reason to question whether the scale is measuring PEM. In a study of 120 MS patients, between 46% and 52% reported each individual PEM symptom, and the overall rate of PEM caseness would have been well over 50% (Jason et al., 2017).

Yet it seems doubtful that MS patients have a PEM experience similar to that of ME/CFS patients. Following an exercise challenge, pain and fatigue were significantly elevated from baseline for at least 48 hours amongst ME/CFS patients, but not for those with MS (White et al., 2012). This is inconsistent with MS patients having substantial levels of PEM.

Further, exercise is promoted by both the National Multiple Sclerosis Society in the US and the MS Society in the UK, in marked contrast to the concerns expressed about the effects of exercise by ME/CFS patients and their charities in both countries. If MS patients experienced PEM as ME/CFS patients do, it seems unlikely that MS charities would promote exercise.

These observations suggest a potentially high level of false positives for the DSQ PEM scale amongst MS patients at least. This is an extremely important issue, because many researchers are now trying to determine the biological basis of PEM, and we hope that more will join them. They will rely on the PEM CDE to determine the presence of PEM not only in ME/CFS patients, but also in comparison groups. Patients with chronic fatigue (as opposed to CFS) and/or healthy people – deconditioned or otherwise – and patients with other chronic diseases such as MS may seem ideal controls. But if the DSQ PEM scale is ascertaining something other than PEM, such as severe fatigue in response to exertion, then false-positive cases will become a serious issue, likely to confound studies into the biology behind PEM.

5. Requirement of frequent and intense PEM for caseness

The DSQ PEM scale asks patients to rate how often and how severely they have had each symptom over the past six months. If a patient has had any symptom with at least ‘moderate’ severity for at least half the time, they are considered to have PEM.

However, as the PEM Subgroup also notes (see below), PEM is triggered by exertion. Therefore, how often and how severely a patient experiences PEM will depend on how often and how much they exceed their trigger threshold. A patient who is so ill that they are largely bedbound and yet who manages to pace themselves and restrict their activity in order to avoid triggering PEM will falsely appear not to have PEM, when assessed by the DSQ PEM scale. Such pacing is extremely common among patients, who use it to avoid the unpleasant and extra-disabling symptoms of PEM.

An analogy made on a patient’s online forum is apposite here, in which the susceptibility to sunburn was compared to the susceptibility to PEM:

‘Some of us have fair skin, and burn easily in the sun. [...] Measuring the size and severity of the burn doesn't reflect the sensitivity of the skin so much as the extent to which a person overdoes things. [...] Surely the measure of skin sensitivity is how much sun can you take before you suffer, not how badly burnt you were last summer?’

Certainly, requiring a symptom to be present for at least half the time seems a very high threshold indeed and is likely to exclude many patients.

It seems likely that this aspect of the DSQ PEM scale would lead to a very significant number of false negative cases for PEM, possibly mingled in with false positive cases who are answering on the basis of other ME/CFS symptoms such as exertion intolerance (see Section 3 above).

6. Patients’ difficulty in recognising their PEM on the DSQ PEM scale

In an online ME/CFS forum discussion of the PEM CDE document, many patients said that they did not feel that the DSQ PEM scale represented their own experience of PEM but that the IOM descriptors did. As far as we are aware, an important absence from the research literature is any study confirming that ME/CFS patients recognise *any* questionnaire description of PEM (a limitation of patient-symptom questionnaires in general).

We therefore set up an online poll, inviting our fellow patients to give their views concerning how the NIH/CDC were planning to measure PEM. It should be noted that although we phrased the poll itself as neutrally as possible, it was

necessary to explain in both the online invitations and in the poll itself that there were potential problems with the NIH/CDC's approach.

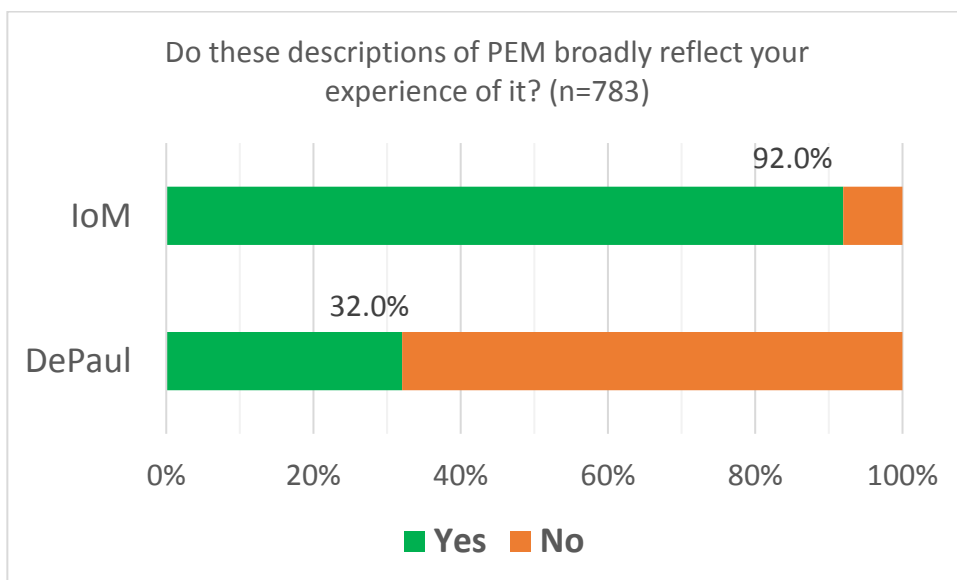
Poll participants did not have to provide any evidence of having ME/CFS in order to take part. The poll ran for five days and 783 people responded.

The poll, reproduced in Appendix 1, presented the IOM descriptors in summary form and the list of DSQ PEM scale symptoms.⁵

When asked, 'Does the DePaul questionnaire description of PEM broadly reflect your experience of it?' 32% of respondents answered 'Yes' and 68% 'No'.

In response to the question, 'Does the Institute of Medicine description of PEM broadly reflect your experience of it?' 92% of respondents answered 'Yes' and 8% 'No'.

The differences in answers to these two questions were large (see figure below) and statistically significant ($p < 0.001$).



The poll had strengths in being both large, reaching over 750 patients, and having been widely circulated on social media, thus probably reaching a much wider and possibly more representative group than researchers or clinicians often do. However, it may have been susceptible to bias, given that it was necessary to mention both in the invitation to take part and in the poll itself that there were some concerns about the DSQ PEM scale. Even if we had not done so, the mere fact that we were conducting a poll at all would have indicated some question over the status quo.

Further, there were over 60 participants in the online forum thread where the DSQ PEM subscale was first discussed and criticised, and the thread may have been read by many others on the 400-strong forum. This content could also have biased the outcome of the poll. The poll's launch was advertised immediately on the forum and 204 people responded during the first, peak eight hours of the poll, most likely including many forum members. 179 people responded during the final three days of the poll, by which time the poll had spread far and wide on social media, where posts did not mention the forum thread. If bias was an issue, we would expect the first group to be more biased against the DSQ PEM subscale than the last group. And indeed, the proportion of patients who thought that the DSQ PEM scale broadly represented their PEM rose from 28% in the first group to 39% in the last ($p=0.27$), while those who thought that the IOM broadly

⁵ The poll results are presented in graphical and tabular form in the file, 'PEM CDE submission from S4ME – Appendix 2', which accompanies this document.

represented their PEM fell slightly from 95% in the first group to 89% in the last. This is evidence for some bias in the survey sample, but also suggests that it is not a huge factor.

In addition, we were not comparing one operationalised list of descriptors with another: the IOM list is a fairly detailed narrative description of PEM, whereas the DSQ PEM items are brief questions designed for a questionnaire. This may have placed the DSQ list at a disadvantage. Nevertheless, there is a very considerable difference in patients' broad recognition of their experience between the two. Even for the respondents in the last three days of the poll, the difference is 50 percentage points (39% vs 89%). And a draft operationalisation of the IOM description by Jason and colleagues and posted by him on Facebook was very well received by patients, indicating that the IOM description works well in multiple forms.

Consequently, we think that the poll indicates that the IOM descriptors were considerably more easily recognised as PEM than the DSQ PEM scale descriptors within our sample of patients, given the size of the difference in the proportion of patients recognising the two sets. The fact that even 61% of late-responding ME/CFS patients polled (and two-thirds overall) do not think that the DSQ PEM scale broadly represents their PEM raises serious questions about its proposed new use as a PEM ascertainment tool.

7. Problems with the proposed 'two-step' PEM determination

As mentioned above, the PEM Subgroup recognise in their document that the DSQ PEM scale may lead to false negatives by requiring symptoms to be present regardless of whether the patient has paced themselves to avoid triggering symptoms. They also consider the possibility of other conditions masquerading as PEM. To deal with these problems, they propose a second step to determine whether a study participant has PEM, as follows (NINDS/CDC, 2017, p.7):

[...] the researcher then evaluates those [DSQ PEM scale] 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 DePaul 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.

This second step appear problematic, for two principal reasons. Firstly, it appears to be 'recommended' (NINDS/CDC, 2017, p.9), not mandatory. Some researchers may not take on the extra burden of asking these additional questions, leaving the DSQ PEM scale as the only means of determining PEM caseness.

Secondly, the second step is not standardised. The researcher may ask any of a variety of questions, phrased in their own way. Given the complex nature of PEM, this is likely to lead to variable case ascertainment.

A further problem with the second step is that it suggests methods of ascertaining PEM that are likely to be unreliable, such as using information from medical records, including those from non-ME/CFS specialists (the Subgroup acknowledge that such records may not reflect an accurate understanding of the nature of PEM).

The 'second step', whether as a supplement to the DSQ PEM scale or on its own, does not, in its present form, appear to be an acceptably accurate means of determining the presence of PEM, even if this step was made mandatory. Moreover, PEM is something experienced by the patient, who will know how much they pace and how it affects their symptoms. The best way to establish whether they experience PEM is surely to use a questionnaire to ask them, and gather the required information in a standardised format, rather than relying on the 'expertise' of researchers or clinicians to make that judgement for them.

Patients' views on what should happen now

Given the problems with the proposals for ascertaining PEM, two questions in the poll of patients asked what the NIH/CDC should do now.

774 out of the 783 patients answered the question, 'Should the working group make a strong recommendation to urgently develop a better questionnaire to assess PEM?' 74% replied, 'Essential', 23% 'Preferable', and 3% 'Unimportant'. 782 answered the question, 'Is it acceptable to use the DePaul questionnaire (supplemented by the researcher-assessment) until a new PEM assessment tool is developed and tested?' 52% replied 'No' (95% confidence interval 48% to 56%), 29% 'Not sure' and 19% 'Yes'.

Thus, nearly all of the patients polled urgently want a better PEM questionnaire to be developed. Around half think the DSQ PEM scale unacceptable to use in the interim and less than a fifth positively regard it as acceptable as an interim measure. This indicates serious problems with the DSQ PEM scale, from the point of view of patients.

Patients' views on how PEM should be ascertained

Many patients (229; 29%) took the option to leave a comment on the poll, and there were many posts on the online forum-thread where the issue of the PEM CDE was first raised. Many of these comments were relevant to what might be included or considered in developing a new PEM assessment tool.

In addition to points that we have already covered in this paper, patients mentioned a number of aspects of PEM – including a great variety of symptoms⁶ – that appear in neither the DSQ PEM scale nor the IOM descriptor list. For example, some patients mentioned feeling initially good during activity, only to find later that it had provoked PEM. Some mentioned that they had rapid-onset symptoms during or immediately after exertion and other symptoms that developed much later. Some questioned whether immediate-onset symptoms were really dysautonomia rather than PEM. Some patients noted that they didn't always recover from episodes of PEM, even after months, but stabilised at a worse level of health than before. Several patients mentioned triggers for PEM other than obvious physical or cognitive exertion, such as noise, light, and both positive and negative emotional events.⁷ Several aspects of terminology were noted as confusing.⁸ There was concern about how to ascertain PEM in patients who are so ill that they may already be over their PEM-threshold while at rest.

Patients also pointed out that, because PEM tends to be delayed, many patients don't make the connection between symptom exacerbation and the exertion that provoked it. They may therefore not recognise PEM in themselves. According to one patient:

'Also, it's really counter-intuitive to feel bad after a delay of 24 hours after exertion. It may take quite some time before people even make that connection, if ever. I only noticed it about three years in, and I hesitated to mention to others because I thought it might make me sound nuts. I wouldn't even discover that PEM had a name for another 25 years.'

Overall, the comments provide patients' insights into their own experience of PEM that go beyond both the DSQ PEM and IOM descriptors and show the importance of including patients in the development of any new PEM instrument.

Conclusions and recommendations

⁶ These included feeling 'wired but exhausted', chills, feverishness, flushing, trembling, dizziness, diarrhoea, temperature dysregulation, visual disturbance, irregularities of blood sugar or blood pressure, shortness of breath, heart palpitations, loss of speech, sensitivity to light, sound and temperature, orthostatic intolerance, and muscle twitches.

⁷ As [...] noted in response to an earlier version of this paper, including triggers that would not normally be considered as 'exertion' might take some of these phenomena outside the scope of PEM as originally (and usefully) conceived. We agree that this is a grey area and one that might benefit from further research. Meanwhile we note that emotional triggers may involve cognition.

⁸ These included being asked about 'exercise' when patients are incapable of this. The use of 'sick' caused confusion, because it can mean 'nausea' in some contexts (and countries) and 'unwell' in others. 'Malaise' was also seen as problematic, since many patients may not know what it means and some thought it had connotations of symptoms being mild or psychiatric. One respondent had concerns over the word 'minimal', noting that for the better-functioning patients, the amount of exertion needed to trigger PEM may be more than 'minimal', but still very low compared to their former level of functioning.

As patients, our motivation is to ensure that any scales used as CDEs for our disease reflect our experience of symptoms, not least as this should lead to more accurate identification of PEM and so to better research.

In this context, the DSQ PEM scale appears problematic as a tool for determining the presence of PEM for many reasons. Its items differ markedly in a number of ways from the IOM descriptors; it allows diagnosis on the basis of single symptoms that might or might not, in fact, be PEM symptoms; factor analysis suggests it may not capture PEM well; it ascertains questionably high levels of PEM in MS patients; it requires PEM to happen intensely and often for caseness, despite the fact that many ME/CFS patients are likely to be pacing to avoid that happening; and only a third of patients polled considered that the DSQ PEM scale broadly reflected their experience of PEM, in contrast to almost all reporting that the IOM descriptors did so.

Taking all these considerations together, we have concerns about the DSQ PEM scale – which was developed as part of an overall ME/CFS scale, not as a standalone instrument validated specifically for identifying PEM.

The field of ME/CFS research needs a PEM scale that has been validated and shown to be sensitive and specific to PEM. Without such a tool to ascertain PEM, ME/CFS's cardinal symptom, all research to reveal the biology of PEM, and of ME/CFS, will be hampered.

This leads us to the following recommendations.

Recommendation #1: Make the funding and development of a new PEM scale the Subgroup's primary recommendation to the NIH/CDC.

We agree with most of the more than 750 patients who answered our poll: namely, that a new PEM questionnaire should be urgently developed. Funding should, of course, be requested as a priority for this development work.

Once the questions have been developed, any new scale would need to be validated, including against a gold standard of patients' and clinicians' experience of PEM and using sick and healthy comparison groups. The new scale would also need to be tested against the DSQ PEM scale to ensure that it was an improvement upon it.

Recommendation #2: Ascertain PEM on the basis of the propensity for it, not its severity and/or frequency

Any new PEM ascertainment questionnaire should focus on the *propensity* for PEM, not its intensity or frequency. There may need to be some minimum level of intensity and frequency in order to rule out false positives such as otherwise healthy people who have had acute viral infections during which they experienced symptoms similar to PEM; or perhaps a question asking how much each symptom limits a person's life, either through the symptom or through having to limit activity to avoid it. This is an issue that needs further consideration, but we certainly recommend the avoidance of setting a high bar such as requiring PEM to be present for at least half the time.

Recommendation #3: Develop the new PEM scale in true partnership with patients.

PEM is complex, and, according to patients' comments in our poll, neither the DSQ PEM items nor the IOM items appear to have fully captured the experience. We believe it is therefore vital that researchers develop the new tool *in genuine partnership* with patients.

We want to see a process that goes well beyond patients simply filling in pilot questionnaires. First, the IOM definition should be the basis for an initial structured but open-ended consultation with patients about what aspects of PEM capture its essence. Second, patients should have the chance to submit question-wordings of their own. Third, researchers should produce a draft questionnaire. And, crucially, fourth, they should then *invite patients' opinions on the questionnaire items*. This latter stage should be done in as many iterations as needed until patients consider that the resulting questionnaire reflects PEM and that they are not having to shoehorn their experience into it.

As far as we are aware, this would go much further than the kind of patient-involvement in developing health outcome measures suggested even by PCORI (the Patient-Centered Outcomes Research Institute; PCORI, 2015). But we believe it is necessary – and not just for PEM, and not just for ME/CFS. The NIH/CDC could break important new ground with this approach, with benefits for many diseases, and the community of ME/CFS patients appear ready and willing to help.

Recommendation #4: Use the DSQ PEM scale with a structured researcher/clinician interview as an interim PEM ascertainment tool

About half of patients polled considered the DSQ PEM scale unacceptable for use until a suitable tool can be developed. We also have reservations about it as an interim measure but consider that it could be useful as part of a revised two-step process until a new scale becomes available. One possibility – though not without its complications – might be to replace or supplement the DSQ PEM scale questions on symptom frequency and intensity with a question such as, ‘Do you reduce your activity to avoid provoking this symptom?’ in order to get at a patient’s *propensity* for PEM as recommended above.

If the Subgroup considers the scale to be an acceptable stop-gap, we strongly recommend that a strict time-limit should be set upon its use.

We noted our earlier concerns with the ‘second step’ of the proposed two-step PEM ascertainment process: that it was optional, unstructured, and could draw upon unreliable information such as earlier diagnoses from clinicians unfamiliar with PEM or ME/CFS.

However, while a validated PEM scale is being developed, we recommend that a structured interview by a clinician or researcher should be quickly developed and used for PEM ascertainment.

In this interview, the interviewer should ask about PEM more globally, rather than just asking about overwork or other possible diagnoses. Such a global question could be based on the Subgroup’s brief description of the IOM definition (see p. 2 of our document), though couched in non-technical language; or on the summary of it that we created for our poll. It should ask about the propensity for PEM, not its frequency or intensity. This global question could be developed very rapidly and given a basic test with patients via an online poll – and, perhaps, with healthy controls, including those recruited by patients. This work could be done in time for late February, 2018.

We recognise that this proposal is not ideal but it seems to us the best interim solution in the current difficult and time-pressured situation. We strongly recommend that this ‘second step’ be replaced in the near future with a properly validated questionnaire and that a timescale be specified for this.

A note of thanks to [...], the PEM Subgroup, and the NIH/CDC

Our concerns about the DSQ PEM scale focus on the Subgroup’s proposed use of it as an ascertainment tool – a purpose for which it was never intended. But without the DSQ PEM scale, there would have been little research on PEM over the years. We would therefore like, in closing, to state again our debt of gratitude – also expressed by many other patients during this process – to Professor Jason and his colleagues for breaking the ground on this extremely challenging topic. We greatly value his work in this area and consider him well-placed to develop a new scale in partnership with patients. We note that he has already begun his endeavours in this direction, building on his long and considerable history of consulting with patients, and we look forward to seeing that work progress.

We would also like to thank the PEM Subgroup for their efforts to provide an appropriate PEM CDE. We and other patients are aware of the difficulty and complexity around this issue, and recognise that creating an appropriate instrument to ascertain PEM has not been, and will not be, an easy task.

Finally, we appreciate the opportunity to contribute to development of key research tools for our disease, particularly this particular measure. We will follow the work on this with great interest.

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Appendix 1: Patient-led poll concerning the DePaul scale

The poll below was posted online and ran between January 18 and 25, 2018.

* * *

Are the NIH/CDC planning to use the right definition of PEM in all their future research?

We are a small group of ME/CFS patients with an interest in research; we include [redacted] and others. We need the help of our fellow ME/CFS patients with an important issue that will affect biomedical research in the US and elsewhere for years to come.

The NIH/CDC are looking for patients' feedback on how they propose researchers should measure aspects of ME/CFS patients' health in all future research – including on how to determine whether a person experiences post-exertional malaise (PEM) and is therefore an ME/CFS patient.

The NIH/CDC propose using a section of Professor Leonard Jason's DePaul Symptom questionnaire to ask about PEM, as it is the only published, relevant research scale currently available. The PEM section asks about the following symptoms:

- Dead, heavy feeling after starting to exercise.
- Next day soreness or fatigue after non-strenuous, everyday activities.
- Mentally tired after the slightest effort.
- Minimum exercise makes you physically tired.
- Physically drained or sick after mild activity.

However, these are different symptoms from those listed in a description of PEM based on the Institute of Medicine report (among other sources) that the NIH/CDC PEM working group has adopted, summarised below (see the working group's full definition [[weblink to PEM Subgroup document](#)]):

- An abnormal response to minimal amounts of physical or cognitive exertion.
- A flare-up of some or all of an individual's symptoms.
- An onset that is immediate or delayed by hours or days.
- A prolonged recovery that can last days, weeks, or months.
- A severity and duration of symptoms that are out of proportion to the initial trigger.
- A loss of functional capacity and/or stamina.

In fact, the DePaul and Institute of Medicine descriptions are so different from each other that they raise the question of which really measures PEM.

The NIH/CDC have some concerns about the DePaul questionnaire and recommend a two-step approach, asking researchers to supplement the questionnaire with a range of possible additional information. For example, the researcher could ask if PEM was previously diagnosed in the patient by a physician (whether or not an ME/CFS expert), or try to judge whether what seems to be PEM might instead be overwork.

However, such an open-ended approach might produce very uneven results and it might be better instead to start with a questionnaire that assesses PEM accurately and does it in a standardised way.

It's crucial that the NIH/CDC assesses the presence of PEM correctly in their future research, or the wrong patients could be studied.

Please help us by saying if either or both of these descriptions describe your experience of PEM. We'll feed the results back to the NIH/CDC.

1. Does the DePaul questionnaire description of PEM broadly reflect your experience of it?

[Yes/No]

2. Does the Institute of Medicine description of PEM broadly reflect your experience of it?

[Yes/No]

3. Should the working group make a strong recommendation to urgently develop a better questionnaire to assess PEM?

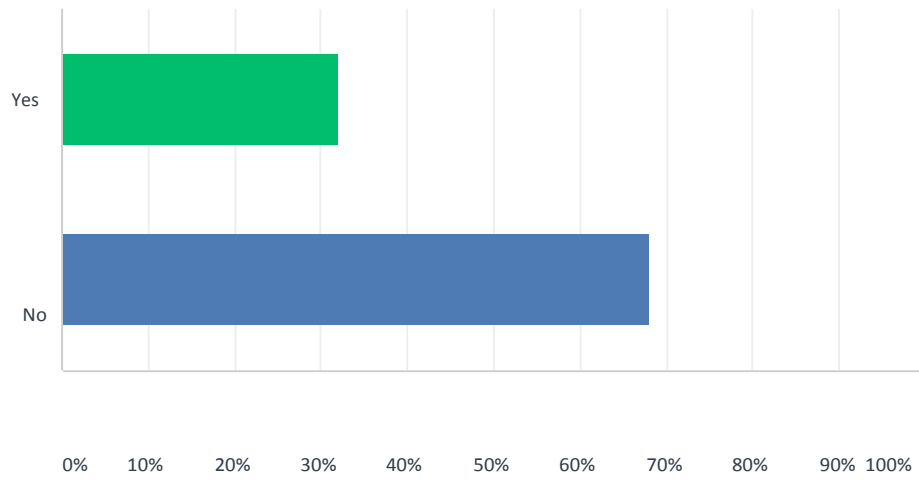
[Essential/Preferable/Unimportant]

4. Is it acceptable to use the DePaul questionnaire (supplemented by the researcher-assessment) until a new PEM assessment tool is developed and tested? [Yes/No/Not sure]

Thanks for completing the survey - results will be posted online after it closes.

Q1 Does the DePaul questionnaire description of PEM broadly reflect your experience of it?

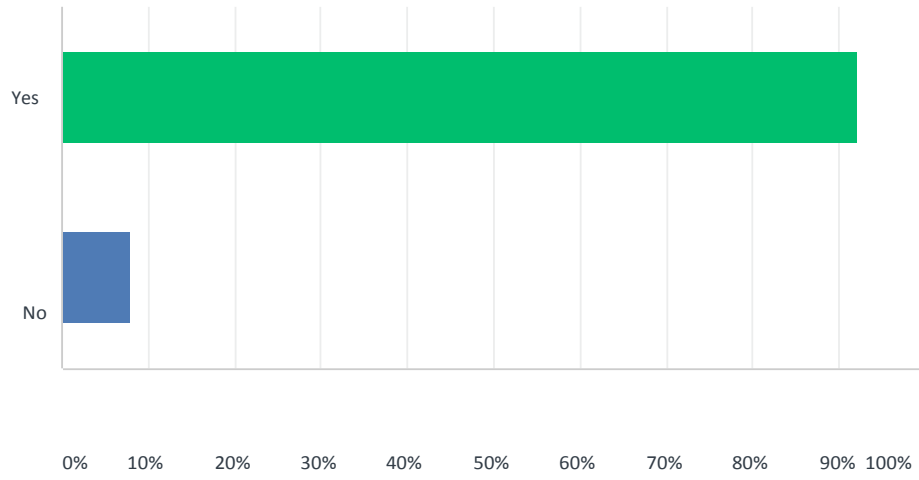
Answered: 783 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	32.06%	251
No	67.94%	532
TOTAL		783

Q2 Does the Institute of Medicine description of PEM broadly reflect your experience of it?

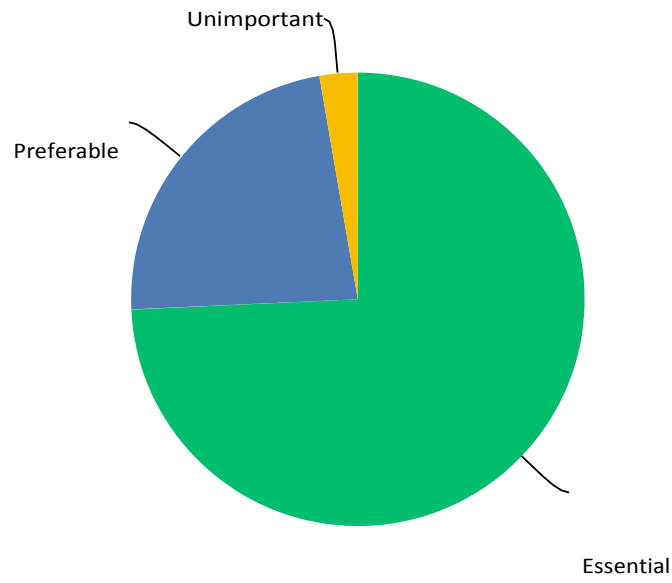
Answered: 783 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	91.95%	720
No	8.05%	63
TOTAL		783

Q3 Should the working group make a strong recommendation to urgently develop a better questionnaire to assess PEM?

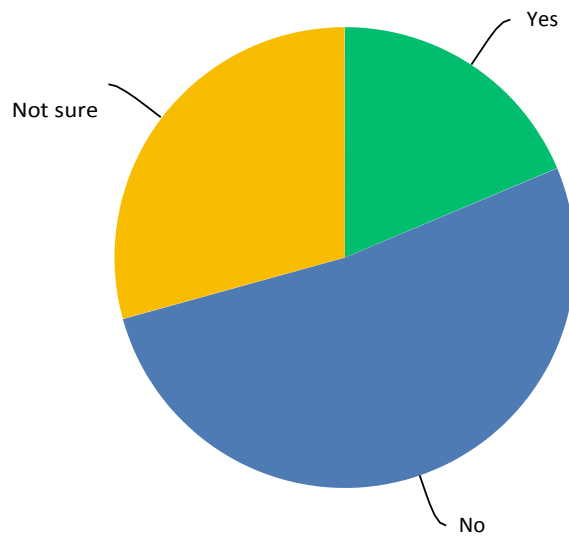
Answered: 774 Skipped: 9



ANSWER CHOICES	RESPONSES	
Essential	74.29%	575
Preferable	23.00%	178
Unimportant	2.71%	21
TOTAL		774

Q4 Is it acceptable to use the DePaul questionnaire (supplemented by the researcher-assessment) until a new PEM assessment tool is developed and tested?

Answered: 782 Skipped: 1



ANSWER CHOICES	RESPONSES	
Yes	18.67%	146
No	52.05%	407
Not sure	29.28%	229
TOTAL		782

Q5 Thanks for completing the survey - results will be posted online after it closes. If you have any further comments, please enter them below. If you'd like a reply, please include an email address, which will remain private. Replies are not guaranteed and depend on the number of comments received and the energy levels available.

Answered: 229 Skipped: 554

[...]

I am requesting that mine to be added to your list of public comments received in response to your Draft ME/CFS Common Data Elements.

I fully endorse MEadvocacy's recommendations as expressed here:
http://www.meadvocacy.org/meadvocacy_s_comment_to_ninds_cdc_cdes_draft_see_what_you_can_do

In brief, "MEadvocacy recommends that:

All federally funded researchers use the ICC which was created by ME experts for diagnostic and research purposes.

- **New questionnaires be designed which are strictly created with ME patients in mind.**
- **PENE be strictly defined as per ICC in order to weed out those who suffer from fatiguing conditions - not ME."**

Thanks you.

[...]

[...]

Public comment on Common Data Elements for ME/CFS

There is a strong need for systematized creation of survey instrument(s) which can be used to compare, correlate and translate diverse findings among different investigators now and in the future. Such instruments are imperative to enable:

1. Continued assessment of ME/CFS v ME v CFS v SEID constructs, so as to better understand
 - (a) whether they represent variants or a spectrum of the same illness as opposed to similar but distinct conditions; and
 - (b) whether they adequately differentiate ME/CFS from other potentially confounding

disorders like lupus and MS;

(c) the underlying mechanisms and how they may interact, especially feedback loops.

These instruments should be able to 1) create a comprehensive map of symptoms, 2) identify defining characteristics, such as PEM, with specificity without imposing top-down assumptions, 3) maintain a detailed database to allow research to be re-evaluated as new findings are published.

2. Generation of a full and detailed map of symptoms based on patient experience should be a priority. Otherwise understanding of underpinning mechanisms will remain elusive. As William Osler said, “Listen to your patient, he is telling you the diagnosis.” The most efficient means of establishing a symptom map is through qualitative means, rather than a questionnaire with lists. A qualitative approach can also be used to help establish individual thresholds, which is a requirement for ME/CFS research.

Examples of this approach would be: “Can you wash your hair?” “Can you stand while having a conversation?” And for those who are very ill, “Can you sit up in bed?” “Can you speak?”

To assess the effects of these activities, patients can then be asked “What happens when you stand and talk at a social gathering?” “What happens when you wash your hair” “What happens when you try to sit up?”

By using a qualitative, conversational method of eliciting information, common speech patterns will emerge that will help define illness severity, identify responses to exertion, and clarify sub-groups based on patient feedback. (This is a bottom up approach, rather than a top down approach.) Of necessity, all responses would have to pertain to the present, rather than over an extended period of time (e.g. several months).

Like other neuroimmune diseases, ME/CFS is notorious for “waxing and waning” symptoms, making assessments over a period of months virtually impossible. Likert assessments are equally as problematic. If a patient experiences insomnia “all the time,” how can researchers measure a worsening of this symptom after exertion or during a clinical trial? It makes better sense to ask a patient how exertions or a drug affects sleep. The answer to an open-ended question leaves more room to pinpoint the types of disturbances that may be influenced by exertion, or medication, or any number of factors that can exacerbate symptoms.

3. Clarifying PEM

At present PEM is included in most contemporary case definitions as a required symptom, however its definition remains elusive. For example, the ICC definition of PEM is “an exacerbation of symptoms following minimal exertion.” What defines “minimal”? For severely ill patients, simply sitting up in bed can exacerbate symptoms. For mildly ill patients who are still in the workforce, staying out too late, running to catch a bus, or having to meet a deadline can produce PEM.

Due to the variability of symptoms, illness severity, and energy levels, activities that are well within the scope of what a patient can accomplish also vary widely, sometimes daily, even hourly. Rather than adopt static parameters of what constitutes “minimal” it is more reasonable to define PEM using personalized points of reference. Asking patients which activities they are no longer able to do without an exacerbation of symptoms, compared to what they could do before falling ill, will yield a threshold.

Another difficulty that arises when measuring PEM is that different types of exertion may produce different consequences. Many patients report that physical exertion produces more severe effects than mental exertion.

Recovery times for PEM due to physical exertion may also be delayed to the point that they may no

longer be considered PEM, but a relapse.

Patients also make a distinction between PEM and a “crash.” PEM is often described as feeling “hit by a truck” following exertion. This reflects a decrease in energy stores. (If one were to imagine that energy stores were money in the bank, PEM would be a balance of zero. A crash, on the other hand, is an overdrawn account.) Crashes are sudden, and they are sometimes described as “every molecule in my body shaking loose.” During a crash, a patient may not experience an exacerbation of symptoms, but rather a complete collapse.

We strongly advise against using the acronym PENE to describe PEM. Pene means “penis” in Spanish. As there are many Spanish-speaking patients and researchers, this acronym is not appropriate.

3. Elucidation of symptoms and dynamics (including cluster phenomena) in a calibrated way. This is important for capture details.

Far more specificity is needed to

- (a) identify and characterize cohort groups/subgroups;
- (b) establish strong management guidance; and
- (c) prioritize avenues of research.

In order to identify cohorts, data must be collected and maintained in a way which allows reevaluation. A case in point is the cytokine research done by Mady Hornig’s group. The researchers identified distinct immune changes in shorter-term patients as opposed to patients who had been ill for a longer period of time. The cut-off for Hornig’s research was three years. If the results had been pooled, this information, which established two distinct cohorts would have been lost. In order to apply findings from research results that establish distinct cohorts, a thorough history of patients, including length of illness, needs to be uniformly implemented. This would allow researchers to re-evaluate findings as new research is published. Information which should be included in background material for subjects of every study are age; gender; level of education, enumeration of previously diagnosed medical conditions, whether ME/CFS acute or gradual onset; believed precipitator or trigger event (e.g., virus or other infection; traumatic accident; toxic exposure; or other _____); duration subject has had ME/CFS; characterization of level of general function with illness compared to pre-illness levels.

Establishing norms for management of data is necessary to facilitate future research. Without stringent requirements for data collection and dissemination, researchers may find their studies weakened through an inability to verify, replicate, or reproduce the results. The inclusion of patient perspectives in establishing cohorts will help remedy this problem.

Research is, by definition, an exploration, which means the field of discovery is virtually limitless. However, in the quest for new information, far too little research is followed up. Over the last three decades many trajectories that could have made a profound effect on patients’ lives have been abandoned for lack of follow up. An re-evaluation of these studies is strongly encouraged in order to prevent every new generation of researchers from “reinventing the wheel.”

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Science Advances, 27 Feb 2015: Vol. 1, no. 1, e1400121 DOI: 10.1126/sciadv.1400121

Respectfully submitted by [...]

[...]

To Whom It May Concern:

I'm not well enough to write my own feedback to the MECFS CDE proposal. Instead, please consider the following by ME Advocacy.

http://www.meadvocacy.org/meadvocacy_s_comment_to_ninds_cdc_cdes_draft_see_what_you_can_d

o Thank you.

Sincerely, [...]

[...].

January 31 2018

**COMMENTS of: [...] Re Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
(ME/CFS) Common Data Elements Project**

**To: National Institute of Neurological Disorders and Stroke (NINDS) and Centers for Disease
Control and Prevention (CDC)**

Via email: NINDSCDE@emmes.com

Dear NINDS and CDC:

The current NINDS Common Data Elements (NINDSCDEs) provides a prime opportunity to bring clarity to the field by contributing to the effort to establish a more complete and coherent understanding of the illness. However, unless a parallel effort is begun with the aim of very precise mapping of symptoms and symptom presentation dynamics, this hopeful project will not be able to fulfill its full potential as a transformational vehicle.

Mapping Project

I strongly urge a parallel effort which might be termed the "Mapping Project." A core component would be to create a series of master survey instruments which could be used to compile the

databases essential to the more precise delineation of the illness and its etiological and physiopathological attributes. The Mapping Project would necessarily involve a collaborative stakeholder approach involving and facilitating more substantial input by the patient community and those involved in public policy in a *systematized* way. I stress the word “systemized” because many previous governmental efforts have sought and achieved important and useful broad stakeholder input, but not in a manner that enables contribution to the state of the science with the requisite level of precision. The present NINDSCDEs invitation for input represents another example of strong outreach, but, again, does not allow for input in a clear, comprehensive and systematized manner.

Many proposed questionnaires and testing methods identified in the various NINDSCDEs have strong components, and the studies done using them may yield fruitful findings. Some of the instruments appear problematic. Yet the cogent point is that, until we have a more detailed map of the terrain, there is no way to validate or invalidate with assurance any particular investigatory method or determination.

The Long Effort to Bring Order to a Diagnostic Mess

Over a decade ago, ME Research UK Chairman Dr. Vance Spence made a presentation in the House of Commons at a hearing of the Group on Scientific Research into ME. Dr. Spence described the absence of full clinical assessment and the conflation of patient populations due to overly vague criteria. He memorably described ME/CFS as a “diagnostic mess”.

In February 2015, after an exhaustive process, the Institute of Medicine (IOM) of the National Academies issued the report of its Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: “Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness” (IOM Report) <http://www.nationalacademies.org/hmd/Reports/2015/ME-CFS.aspx>. The IOM Report notes that, for decades, clinicians and researchers developed separate case definitions and diagnostic criteria for ME, CFS and ME/CFS. For example, an advisory committee to the CDC advocated US adoption of the Canadian Clinical Working Case Definition, more widely known as the Canadian Consensus Criteria (CCC). The CCC used the umbrella term “ME/CFS.” However an international group consisting of many of the same clinicians, researchers and teaching faculty which produced the CCC, updated their concept and advanced Myalgic encephalomyelitis: International Consensus Criteria (ICC) as more appropriate research criteria, arguing its improved encapsulation of underlying pathophysiology and greater consistency with the classification of ME in the World Health Organizations’ International Classification of Diseases (ICD G93.3). The IOM Committee employed the currently prevalent umbrella term “ME/CFS” and advocated for changing the name of the disease to “Systemic Exertion Intolerance Disease” (SEID). The IOM Report also proposes new diagnostic criteria. As the IOM Committee emphasizes in its Report Brief accompanying the IOM Report, this new criteria was conceived with the aim of having “clear and concise diagnostic criteria that will facilitate diagnosis and care for the patients affected by this often-debilitating disease. Broad dissemination and use of these criteria is essential to improve understanding of the disease among health care providers and the public and provide a firm foundation for future improvements in diagnosis and treatment of these patients.” In addition, the IOM Report called for a new independent code to be assigned for the disease.

The IOM Committee's remit was to come up with updated core diagnostic criteria. The IOM Report appears to be helping bring some clarity to the diagnostic mess. But this begs the question: Now what?

Still Desperately Needed: Far More Precise Cohort & Illness Elucidation

At this point, regardless of whether the illness is called ME/CFS or SEID, we are advancing towards a much stronger understanding of the basic form, shape, and dynamic processes of this disorder. There appears to be general consensus that ME/CFS/SEID is a complex, multisystem, multi-symptom disorder involving profound dysregulation of homeostasis and characterized by dysfunctions of the central nervous system; autonomic system; immune system and cellular function/signaling. Unique features of the disorder include specific patterns of symptom presentation, specific types of negative feedback loops, recurrent feelings similar to a low-grade flu, significant levels of fatigue, and recurrent episodes of extreme loss of stamina.

The IOM Report was an important step, but unless clinicians and research investigators are incentivized – or at least guided – by the NIH, NINDS, and CDC to more precisely delineate symptoms and presentation dynamics, resources and time will be wasted as field participants wander and retread circles.

Conclusion

The NINDSCDEs presents a prime opportunity to truly advance the field by filling in important details. Absolutely crucial to this process is enabling patients to better inform the experts. Doctors know medicine. Researchers know testing methods. Only patients really know their own illness experience.

I urge NINDSCDEs to initiate or otherwise support a Mapping Project to facilitate ongoing integration of symptom-specific details into the understanding of this illness. A critical aspect of the project would be creation of novel survey and other instruments (for example graphics) to more thoroughly represent the actual experience of the patients themselves.

A final point is that, given the exceptionally multisystem, multi-symptom nature of ME/CFS/SEID, such a project would inevitably contribute to the understanding of other illnesses, and might serve as a model for similar exploratory projects of other chronic conditions.

Thank you for your kind consideration.

These comments represent my personal opinion, and do not represent any position held by any organization with which I am affiliated.

[...]

NINDS CDE Project
c/o Dr. Vicky Whittemore & Dr.
Elizabeth Unger 9000 Rockville Pike
Bethesda, MD 20892

RE: Pre-release Version 0.0 Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Dear Drs. Whittemore & Unger:

The Solve ME/CFS Initiative (SMCI) commends the Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Common Data Elements (CDE) Working Group and the National Institute of Neurological Disorders and Stroke (NINDS)/Centers for Disease Control and Prevention (CDC) CDE Team on the ME/CFS CDE project. The objectives of this collective effort and the transparency of the process is a promising step towards progress in ME/CFS research.

Defined data standards will enable numerous improvements to ME/CFS research methods and clinical approaches. This disease needs a common language and universal standards to facilitate comparison across studies, improve clinical trial design, define a natural history of the disease, and to refine an accurate clinical definition – the CDEs set us on the path to accomplish these goals. Importantly, they will greatly strengthen efforts that are underway nationally, like the NIH ME/CFS Collaborative Research Centers and Data Management and Coordinating Center, and help incorporate commendable work done by different groups.

SMCI participated alongside many stakeholders to provide input during the development of the CDEs through direct representation on the Baseline/Covariate Information and Neurologic/Cognitive/CNS Imaging subgroups. We commend the openness of the process via the opportunity for public review and comment from the ME/CFS community. The development of the CDEs was greatly strengthened by a consortium of contributors working together and the solicitation of invaluable input from stakeholders.

The CDEs are an important component of the push for a broad and collaborative research network and an integrated approach to data collection, management, and use in ME/CFS research. SMCI strongly supports this effort and encourages continued collaboration and wide adoption of the CDEs.

Thank you for your dedication and the steps you have taken to improve federal standards and support for ME/CFS research. Please also convey our commendations to the entire CDE team.

SMCI is a non-profit disease organization that works to accelerate the discovery of safe and effective treatments, strives for an aggressive expansion of funding for research that will lead to a cure, and seeks to engage the entire ME/CFS community in research.

Sincerely,

[...]