February 10, 2016

Questions regarding the NIH Clinical Center "PI-CFS" Study Protocol from ME/CFS patient community

NIH Intramural study http://clinicalstudies.info.nih.gov/cgi/wais/bold032001.pl?A_16-N-0058.html@chronic@fatigue@syndrome@@

We recognize the importance of the NIH intramural study to advancing this field and want this study to be successful as much as NIH does. These questions are provided to clarify the intent and in the spirit of ensuring the success of this study. We know that NIH is already working on clarifying some of these issues and we look forward to hearing more about the study.

1. **General questions about the study:**
   (1) The current NIH clinical research studies site states that you are "currently recruiting." Has recruitment started already and what is the plan for recruitment (e.g. geographic area, methods of reaching potential subjects (e.g. online, clinic-based, support groups, etc.)?
   (2) Will you provide a link to the current versions of study protocol (with amendments) and the patient consent documents? We appreciate that these can change over time but believe that a link that points to the most recent version would ensure that the information is always up-to-date.
   (3) Can you clarify what protocol changes require IRB approval?

2. Engagement of the community

- What ME experts advised you on this protocol? If none, why not? Did they agree to the use of the Reeves criteria and the rest of the protocol?
- How will ME/CFS experts, particularly those who regularly diagnose ME/CFS patients, be involved in the selection of patients? Ideally, given the lack of diagnostic gold standard, even across the CDC multi-sites, two such ME/CFS experts would be involved in reviewing each case and pick the cases where both agree.
- Who will be on the executive committee overseeing this study and the research team designing and conducting the study? How will ME/CFS experts outside of HHS, particularly those who have regularly treated patients and researched and published in this disease, be involved in the executive committee and the research team designing and conducting the study? As discussed by Dr. Rowe at the FDA in 2013, study design issues with this disease are complex and long experience and deep knowledge of the disease is important to understanding those issues.

3. Disease Name

- The disease is referred to as "PI-CFS" but the term "CFS" refers to a broad range of definitions, which do not require PEM and have been shown to include patients who do not have the disease. Further, the IOM recommended that the disease not be referred to as "CFS." Given that the NIH has said that PEM is mandatory, we recommend that the disease not be referred to "CFS" and instead that term "PI-ME/CFS" or "PI-ME" be used. Is there any reason that that can not be done?

4. Study Objective

- The current protocol states that the study objective is to "learn more about PI-CFS." If we understand correctly, the posted protocol might not have been finalized. Will there be a fuller explanation of the study objective?

4. Subject selection criteria

We want to see this study succeed as much as NIH. Prior studies of ME/CFS have yielded inconclusive, inconsistent, and even contradictory results. While some of this might come down to the

nature of the disease itself, one distinct reason for these results might be because of the case definition used (i.e. it is not specific enough) and/or the methods used to ascertain if/ how subjects fit those definitions. This not only confounds research, but also hurts patients as findings from Oxford and Reeves 2005 studies have been inappropriately applied to CCC or ME-ICC patients.

As originally posted, the NIH protocol specified that it was using the Reeves 2005 definition. We are glad to hear that the NIH study is going to require PEM and we also understand that NIH expects that subjects with meet the CCC and the IOM criteria.

- Will the current protocol be modified to explicitly require PEM?
- Will the protocol explicitly require that subjects meet the Canadian criteria? If not, how will the protocol insure that patients meet CCC, since, as currently specified, the Reeves/Fukuda list of symptoms is what is required for inclusion, not the symptoms specified for the Canadian Consensus Criteria.
- The current protocol states that it is using the Reeves 2005 criteria and in response to an initial question, the NIH stated that the protocol was using a "modified Reeves" criteria. But Reeves does not require PEM, has increased prevalence 6-fold over commonly accepted estimates, and has resulted in what the IOM described as an overpresentation of depression and PTSD. Referring to this study as "Reeves 2005" or "modified Reeves" will create confusion on what patients were studied in this trial. Would NIH consider removing the reference to "Reeves 2005?" If not, why not?
- We understand that there was a typo in the functional impairment inclusion criteria listed in the protocol and that should have been listed as "less than," not "greater than." The other issue is that the Reeves functional impairment criteria only require impairment on any one scale, including the "role emotional" scale. As Dr. Jason has noted, this could result in the selection of patients with mental illness but not ME/CFS. Further, he found that "the SF-36 Vitality, Social Functioning, and Role-Physical subscales have the best sensitivity and specificity."[1] Shouldn't the functional impairment criteria at least be revised to not include subjects who only exhibit "role emotional" impairment?
- The protocol states that subjects with various mental disorders are allowed as long as they are managed on a stable treatment for 6 months. How will the study confirm that the symptoms satisfying case criteria are not the result of that mental illness? (Note that this is a particular concern in the protocol as posted on February 7, 2016 but may not be an issue if subjects have PEM and meet CCC)
- Why does the study not include patients with disease duration longer than 5 years? Many patients are ill for decades. Additionally, it is known that short duration patients with post-infectious fatigue can recover spontaneously. Will the study track the short duration patients longitudinally to see whether their study diagnosis of PI-CFS resolves? How long will longitudinal tracking continue?
- In this 2012 paper,[2] CFSAC members and Dr. Unger of the CDC recommended that in future studies, inclusion and exclusion criteria and the method of ascertainment of inclusionary and exclusionary criteria, including the cut-off values for diagnostic tests, be clearly stated (e.g. whether exclusionary diagnoses are patient self-report vs. physician-diagnosed/ screened, what methods were used for screening for depression, what blood tests were used, etc.). Stating these factors clearly allows researchers to be able to replicate and also compare studies later. When not possible to list all exclusion criteria, it would be good to have information on WHY

[1] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3170036/
[2] http://www.ncbi.nlm.nih.gov/pubmed/22306456

subjects were excluded; too many studies are vague about exclusions or don't report this data. Does this study have such protocols in place and will this information be made public?

- In prior studies using Fukuda criteria, subjects have merely been classified as fitting Fukuda or not and no data is shared or reported on HOW the subject fits Fukuda, especially in regards to WHICH of the 8 symptoms they have. Dr. Luis Nacul's presentation at NIH last year[3] discussed how subjects fitting Fukuda could have any of 165 different combinations of symptoms. (This applies to Reeves also as it uses the same symptom criteria as Fukuda). Thus, using Fukuda itself, even properly, can generate much subject heterogeneity. Furthermore, as newer case definitions are created (such as the CCC and the IOM criteria), having more information about symptom breakdown allows the data to be re-examined using new criteria. Will this study include a breakdown of how each subject fits the symptom criteria of Reeves/Fukuda? Will it include other symptoms not considered by Fukuda (e.g. orthostatic intolerance)?
- Exclusionary diagnoses need to be considered very carefully. For example, if hypothyroidism and orthostatic intolerance, very common co-morbidities, are considered exclusionary, a large number of subjects will be excluded and the results of any study may not be generalizable to the average patient. There is considerable overlap between fibromyalgia and ME/CFS in symptoms yet subjects with both disorders might be different from subjects with only ME/CFS. Will the design or analysis of the study take into account those with FM also vs. those with only ME/CFS? This issue also needs to be taken into account for depression subtypes other than psychotic depression since this study includes subjects with and without depression.
- NIH has stated that the plan is to include patients from one of the CDC multi-sites. Assuming there is a possibility that subjects can come from other sources, will the study specifically exclude somatoform illnesses? This is important because "CFS" is often stated as an exemplar of somatoform illness in papers on somatoform illness. Again, this is a particular concern in the protocol as posted on February 7, 2016 but may not be an issue if subjects have PEM and meet CCC.
- Many patients with severe neurological impairment have been diagnosed with functional or psychosomatic conditions, somatoform disorder or conversion disorder. Also, many ME patients have "pseudo seizures." If subjects with such previous diagnoses are automatically excluded from the PI-CFS cohort, it could exclude many severe ME patients. How will the study deal with that?

5. **Symptom assessments - screening subjects/ outcome measurements**

- How will each of the symptoms be assessed? What specific measurement tools ***and*** tests, including objective tests, will be used?
    - For PEM specifically: We understand that PEM will be required and that it will be objectively measured. How is post-exertional malaise being defined? What specific instruments and objective tests will be used to assess its presence?
- Jason's studies show the importance of assessing not just the presence of a symptom but the severity and frequency as well, leading the IOM criteria to require that the symptom must be present at least half the time and at least of moderate severity. Will symptom assessment in this study include not only presence but also severity and frequency?
- Why is the CDC symptom Inventory being used? Does the CDC Symptom inventory ask about both symptom frequency and symptom severity as recommended by the IOM criteria and does it include symptoms that are core to both the CCC and the IOM criteria (e.g. orthostatic intolerance)?
- Is the DePaul Symptom Questionnaire being used? If not, why not? The reason for asking is that it covers the major symptom classes of the disease, covers the need to frequency and severity of

[3] https://prevention.nih.gov/programs-events/pathways-to-prevention/past-workshops/me-cfs/agenda

symptoms, has been validated across various national and international patient cohorts, and used in various studies comparing definitions.

- Will the exercise protocol use the two-day cardiopulmonary exercise test with gas exchange measurement as practiced by Snell, Stevens, and Keller? If not, why not?
- What instrument will be used to perform the mental health assessment? Is the instrument appropriate to patients with chronic physical illness?

5. Study design

- How many subjects will be included in each of the four study groups? Have sample size calculations been made to assure that adequate numbers of subjects have been recruited in order to yield valid results as possible? We ask because, while the NIH noted that all PI-CFS subjects will have PEM and will meet CCC and IOM criteria, Dr. Rowe discussed (at the ME/CFS FDA meeting in 2013) the need for larger study sizes because of the complexity of study design issues with this disease.
- Could you confirm that the set of lab tests being done will be done both pre-exercise and also post-exercise. If not, what tests will be done both pre and post-exercise (including cognitive and physical)?
- Is there a specified interval between initial assessment and in-patient stay?
- Given the exercise tests, are there any mechanisms to allow inclusion of severely ill patients?
- Why were the Lyme Infection Asymptomatic Group and the Functional Movement Disorders chosen as ill controls? What do you hope to learn by comparing ME/CFS to those groups?
    - Why was the functional movement disorders group chosen? It is true that secondary depression is a comorbidity but that is true in many chronic illnesses. Is it considered standard practice to use a psychological disease as a comparison group in such a study in other chronic illnesses? What learning is the NIH hoping to get from comparing ME/CFS to FMD?
    - Why were diseases like MS or diseases with neuroinflammation not chosen as controls given e.g. evidence of neuroinflammation in the Nakatomi neuroinflammation study[4] and the evidence of neurological disruption seen in the Zinns' qEEG study?[5]

[4] http://dx.doi.org/10.2967/jnumed.113.131045
[5] https://sciforschenonline.org/journals/clinical-research/CLROA-2-110.php