The Need for Consensus on ME/CFS Research Case Definitions.
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At the October 2016 IACFS/ME Conference, the CDC and NIH held a session on a planned initiative to establish common data elements (CDEs) for ME/CFS. The goal of this initiative is to standardize the collection of data across studies to facilitate comparison of results. For a field that has suffered from a lack of standardization, this is an essential step to improving cross-study comparability. But Health and Human Services (HHS) staff also stated that as long as researchers use common data elements, it would not matter what research case definition they use. This is concerning because requiring that standardized data be collected on the presence or absence of a hallmark symptom such as post-exertional malaise (PEM) is not the same thing as requiring that patients have these hallmark symptoms in order to be diagnosed as ME/CFS patients. The critical question that must be asked is whether CDEs alone will compensate for the continued ambiguity on what core inclusion and exclusion criteria are required for the selection of ME/CFS research cohorts.

This lack of agreement on patient selection criteria has plagued ME/CFS for decades, confounding research and resulting in inappropriate clinical guidelines that have misled doctors and harmed patients. Brurberg reported that there are 20 different case definitions and that prevalence estimates range from 0.01% to 2.60% and even higher, indicating the magnitude of the problem. Worse, these definitions are sometimes modified in ways that further expand the conditions given the "ME/CFS" label. One example is the 2011 PACE trial, which stated it used the Fukuda definition to characterize patients but only required Fukuda's four symptoms to be present for one week instead of the required six months.

Many groups have identified the definitional non-specificity and inconsistency as a priority issue:

- The 2011 NIH State of Knowledge Workshop noted that the lack of agreement on how patients were being selected was harming the "entire scientific enterprise" and prioritized the need for a common and specific research case definition.
- In 2012, HHS's CFS Advisory Committee deliberated on the case definition problem and recommended that a workshop of stakeholders be convened to reach consensus on a case definition, beginning with the 2003 Canadian Consensus Criteria (CCC).
- In a 2014 letter to HHS, fifty international disease experts highlighted the problems with Fukuda's lack of specificity and called on HHS to adopt the Canadian Consensus Criteria.
- The 2014 AHRQ Evidence Review highlighted both the lack of specificity of some definitions and the inconsistencies across definitions. It called for Oxford to be retired and recommended that future studies "use a single agreed upon case definition."
- In 2015, the Institute of Medicine identified systemic exertion intolerance as the core symptom of ME/CFS. It noted that Fukuda and the 2005 Reeves definition (also called the empirical definition) include patients who do not have ME/CFS and that the 2005 Reeves definition produces "a biased sample with overrepresentation of individuals with depression and posttraumatic stress disorder."
- The 2015 Pathways to Prevention (P2P) report stated, "Variability in inclusion and exclusion criteria such as the case definition… has significantly hampered progress." P2P recommended that a "team of stakeholders (e.g., patients, clinicians, researchers, federal agencies) [be assembled] to reach consensus on the definition and parameters."

- The December 2016 HHS "Federal Partners" response to the P2P report noted that the use of different case definitions had caused "confusion and the inability to draw correlations across studies" and concluded that the lack of clearly defined diagnostic criteria was a "key impediment" to ME/CFS research.

The research community has taken steps to address this issue. Dr. Leonard Jason has published extensively on the deleterious impact of non-specific research case definitions. Experts have published the 2003 Canadian Consensus Criteria and the 2011 ME International Consensus Criteria (ME-ICC), both of which require hallmark symptoms such as PEM and cognitive dysfunction and exclude conditions like somatoform illness and other primary mental illness allowed by Fukuda, 2005 Reeves, and Oxford. And increasingly, published biomedical literature, including many of the exciting recent publications, use either the CCC or the ME-ICC to select patients for research while the London Biobank requires that ME/CFS patients meet the Canadian Consensus Criteria.

Given these facts, it is surprising that the Federal Partners report on the P2P report concluded, "more research is needed before a case definition can be established." In explaining the challenges with research, the report noted that one P2P participant had said there were "163 possible combinations of symptoms associated with the disease." But that P2P participant, Dr. Luis Nacul of the London School of Hygiene and Tropical Medicine, was not taking about the heterogeneity of the disease. He was talking about the heterogeneity of Fukuda, noting that there are 163 different combinations of Fukuda's "any 4 of 8" symptoms. Of these combinations, only 35 (20%) include ME/CFS's hallmark PEM, begging the question of what other conditions are being swept up in a Fukuda diagnosis. Dr. Leonard Jason amplified this point, noting that in a review of 53 Fukuda studies, as few as 25% of participants in a given study had PEM. Dr. Nacul recommended that researchers require that patients meet both Fukuda and the CCC to be given a diagnosis of ME/CFS, at least until biomarkers could be validated. He was not proposing waiting for more research.

The idea that any research case definition can be used to select ME/CFS patients as long as common data elements are used raises significant concerns. Will Fukuda or the 2005 Reeves still be used to select ME/CFS cohorts, even though we know they select patients who do not have ME/CFS? Will patients selected with the NICE criteria, currently planned for a large U.K. study, be considered ME/CFS patients? (NICE requires fatigue plus one other symptom and while PEM is listed as key, the worsening of symptoms following exertion characteristic of PEM is defined as optional.) If the IOM criteria is used, will somatoform illness be excluded? Will any combination of inclusion and exclusion criteria be accepted as a valid way to identify ME/CFS cohorts?

The use of disparate and non-specific research case definitions is responsible for the muddle we face today. Continuing to use ***any*** case definition to select ME/CFS patients will perpetuate this problem, particularly as new researchers enter the field. While essential, common data elements alone will not solve this problem, as many of the studies will be accessed through published literature and evidence reviews, not through a database. But even if all studies were suddenly in a single database built on common data elements, the man-made heterogeneity introduced by including disparate, unspecified conditions in ME/CFS cohorts will impede the significant progress that would be possible if patients labeled as ME/CFS actually have ME/CFS.

The NIH and CDC are to be applauded for convening a group of researchers to reach consensus on common data elements. This is an important step. But for the ***first step***, NIH and CDC should work

with researchers to reach consensus on what research case definition – or at least what core inclusion and exclusion criteria – will be used going forward. And just as importantly, explicit consensus should be reached on what research case definitions will no longer be accepted for selection of ME/CFS cohorts. Achieving this consensus will accelerate research by helping to ensure that all researchers, including those just entering the field, are studying the same disease.