HHS Public Access

Author manuscript

Brain Behav Immun. Author manuscript; available in PMC 2015 November 13.

Published in final edited form as:

Brain Behav Immun. 2012 March ; 26(3): 401–406. doi:10.1016/j.bbi.2012.01.014.

Minimum data elements for research reports on CFS☆

Leonard A. Jason[a,*], **Elizabeth R. Unger**[b], **Jordan D. Dimitrakoff**[c], **Adam P. Fagin**[c], **Michael Houghton**[d], **Dane B. Cook**[e,f], **Gailen D. Marshall Jr.**[g], **Nancy Klimas**[h], and **Christopher Snell**[i]

[a]DePaul University, United States

[b]Centers for Disease Control and Prevention, United States

[c]Harvard University, United States

[d]University of Alberta, Canada

[e]William S. Middleton, Memorial Veterans Hospital, Madison, Wisconsin, United States

[f]Department of Kinesiology, University of Wisconsin-Madison, Madison, Wisconsin, United States

[g]University of Mississippi Medical Center, United States

[h]University of Miami, United States

[i]University of the Pacific, United States

Abstract

Chronic fatigue syndrome (CFS) is a debilitating condition that has received increasing attention from researchers in the past decade. However, it has become difficult to compare data collected in different laboratories due to the variability in basic information regarding descriptions of sampling methods, patient characteristics, and clinical assessments. The issue of variability in CFS research was recently highlighted at the NIH's 2011 State of the Knowledge of CFS meeting prompting researchers to consider the critical information that should be included in CFS research reports. To address this problem, we present our consensus on the minimum data elements that should be included in all CFS research reports, along with additional elements that are currently being evaluated in specific research studies that show promise as important patient descriptors for subgrouping of CFS. These recommendations are intended to improve the consistency of reported methods and the interpretability of reported results. Adherence to minimum standards and increased reporting consistency will allow for better comparisons among published CFS articles, provide guidance for future research and foster the generation of knowledge that can directly benefit the patient.

Keywords

Minimal data elements; CFS

☆The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

*Corresponding author. Address: 990 W. Fullerton Ave., Suite 3100, Chicago, IL 60614, United States. Tel.: +1 773 325 2018. LJason@DePaul.edu (L.A. Jason).

1. Introduction

Chronic fatigue syndrome (CFS) is estimated to affect about a million Americans, and to cause considerable disability and economic costs to society (Jason et al., 2008; Lin et al., 2011). According to the 1994 International Research case definition (Fukuda et al., 1994), individuals diagnosed with CFS must have six or more months of persistent fatigue as well as four or more cardinal symptoms that did not predate the onset of the illness (i.e., lymph node pain, sore throat, muscle pain, joint pain, postexertional malaise, new or different headaches, and unrefreshing sleep).[1]

Variability in the description of basic information on sampling methods, patient characteristics, and clinical assessments in CFS research reports has been a major impediment to replicating findings across studies. To reduce heterogeneity, accurate measures and key descriptors and symptoms must be reported for the selected patients with CFS. A recent article that reviewed publications on the genetics and epigenetics of fatigue in adults reported that phenotypic heterogeneity and the lack of a uniform systematic approach severely limited the findings from those studies (Landmark-Høyvik et al., 2010). The issue of variability in CFS research was also recently highlighted at the NIH's 2011 State of the Knowledge of CFS meeting (2011) prompting researchers to consider the critical information that should be included in CFS research reports. Two factors contribute to the confusion, the heterogeneity of the phenotype and the likely hypothesis that there are multiple underlying etiologies giving rise to the clinical entity known as CFS (Klimas and Koneru, 2007; Komaroff, 2000). Thus, it would be both scientifically and clinically useful and informative to sub-categorize patients according to disease-relevant variables including clinical criteria, co-morbidities, biomarkers etc. Clearly, a consensus on the provision of data collection details and measures used in CFS research is needed.

Oftentimes, limited clinical (and even laboratory) information is presented in CFS scientific articles. Available checklists for describing phenotypes have considerable overlap, contain arbitrary variations in wording and structuring and are applied inconsistently in various CFS research communities. There is a significant need for improved standardization procedures and increased communication across research groups. In fact, there is already a greater push within the biological and biomedical communities to create minimum reporting guidelines for publication of CFS research results. For instance, the Minimum Information for Biological and Biomedical Investigations (MIBBI) project which serves as a compilation of "minimum information checklists" that outline the key information needed for reporting results of experimental studies using specific techniques (e.g. fMRI studies or studies using cellular assays) (Taylor et al., 2008). The purpose of this article is to provide a framework for improving consistency of what is reported in CFS research and to ensure that appropriate scientific standards are met. In addition, we suggest validated instruments and procedures

[1]In contrast, the term Myalgic Encephalomyeliti (ME) is used in a number of European countries, and ME often refers to patients who have an acute onset and have symptoms within the three major ME categories (i.e., post-exertional malaise, neurological manifestations, autonomic manifestations) (Goudsmit et al., 2009; Hyde, 1999; Jason et al., 2012; Ramsay, 1988). Carruthers et al. (2011) have recently proposed an international consensus definition of ME. Although comparative data is limited at this time, in general, those with ME have more functional impairments, and more severe physical and cognitive symptoms than those with CFS (Jason et al., 2011a). Because the vast majority of research studies have used the Fukuda et al. criteria, in this article, we will refer to patients with this illness as having CFS.

that could help build consensus with respect to research methods. We present our consensus on the minimum data elements that should be included in all CFS research reports, along with additional elements that are currently being evaluated in specific research studies that show promise as important patient descriptors for subgrouping of CFS. The information on the additional elements should be useful for guiding researchers interested in specific areas of CFS research (e.g. brain, immune, autonomic nervous system, etc.). We recommend that as many of the following tests/criteria as possible be included in order to better define and standardize patient populations between studies.

2. Minimal essential elements

A brief summary of the minimal data elements recommended for CFS research reports is included in Table 1. Some of the elements, such as study design and participant demographics, do not differ significantly from those expected for research reports involving human subjects. The study design frames the kinds of questions that can be addressed. The report should indicate whether the analysis was part of the primary hypothesis, or a secondary analysis, *ad hoc* or *post hoc*. The site of enrollment (particular type of clinic or community) may also impact the results and the generalizability of the findings. For clinical trials, there are internationally accepted standards for reporting, like CONSORT, and they should be considered when reporting trials (Schulz et al., 2010). Many major medical journals will not accept articles about trials that do not contain all/ most of the CONSORT elements. Another paper is being written concerning the domains of this illness as well as specific reliable and valid instruments to use to measure these domains (fatigue, pain, sleep disturbance, etc.).

Standard demographic information such as age, sex, race and ethnicity provides basic information about the study population. The additional demographic characteristics listed in Table 1 have all been found to be important in CFS studies. Some, such as body mass index (BMI), socioeconomic status, insurance, living arrangements, may be associated with risk for illness (Friedberg and Jason, 1998; Jason et al., 2003). Other variables, such as mode of onset and duration of illness are important to a subgroup of patients with CFS. In particular, acute versus gradual onset have been consistently noted to be important in stratifying disease. However these terms do not have accepted definitions, so it is essential that investigators specify what approach was used to make the distinction. The specific questions or methods used to determine mode of onset should be cited (if previously published) or be provided in supplementary material. Duration of illness is an important characteristic, as increasing time from onset increases the potential for secondary co-morbidities to develop (Friedberg et al., 2000). Factors that exacerbate or trigger illness are of interest, although not necessary for all studies. One might also ask about the episodic nature of the illness and the perceived periodicity of symptoms and periods of relative remission. If the information is provided, the method of collection (i.e. specific questions, approach to summary) should be provided.

Whenever information is collected via questions or questionnaires, the method of administering these should be provided; for example given by interviewer over telephone or in person, self-administered written or on-line. Questionnaire should be provided as

supplementary material along with scoring method, or if fully described in publications, the citation given. In the case of published instruments, any change in format or scoring should be noted.

The case definition used to enroll patients should be specified (see footnote 1). In addition, the method used to apply the case definition should be indicated. Parts of case definition are often gathered through symptom inventories. Symptoms probed should include post-exertional malaise, unrefreshing sleep, impaired memory or concentration, muscle pain, multi-joint pain, headaches, tender cervical or axillary lymph node, and sore throat. Additional symptoms may be in neurologic, autonomic, neuroendocrine, immune areas. Examples of symptom inventories used in CFS studies include the DePaul Symptom Inventory and the CDC Symptom Inventory. Until there are specific diagnostic markers for CFS, the diagnosis remains one of exclusion. While patients with exclusionary conditions, i.e. those that could contribute to reported symptoms, are managed clinically as CFS, there is still debate about whether treatable medical conditions could bias or mask the underlying biology of CFS. There have been some attempts to gain consensus on which medical conditions should be considered exclusionary (for example, Reeves et al., 2003). If a previously published list is used, this may be cited. If not, the list of specific conditions used to exclude CFS should be provided. For example, one study might recruit only individuals with specific symptoms, such as Orthostatic Intolerance, and this needs to be noted. In addition, the method of ascertaining these conditions should be provided (as an example, asking about history of liver disease versus laboratory evaluation of liver function tests (LFTs) or hepatitis panel). Patients with CFS often have several co- morbid conditions (e.g. irritable bowel syndrome (IBS), interstitial cystitis/ painful bladder syndrome (IC/PBS), chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), vulvodynia, endometriosis (Rodriguez et al., 2009). Those should be elicited and listed separately in an effort to obtain a more refined phenotype. If laboratory tests are used, it would be useful to list which tests or published criteria were used and what constituted an exclusion. Importantly, were controls evaluated in the same way as CFS cases?

Medications can modulate or exacerbate symptoms and can influence measures that may be part of the study protocol, for example beta-blockers influence heart rate variability. Studies should specify if medication history was obtained, and if so, how (prescription and non-prescription). Special attention needs to be paid to dietary supplements that the patient might be using or has used (e.g. licorice inhibits 11 beta-hydroxysteroid dehydrogenase (type 2), HSD11B2, and might result in the so-called “apparent mineralocorticoid excess syndrome”)

Functional impairment is a central to the illness, and the method of determining this should be provided. Standardized instruments useful for this include Sickness Impact Profile (SIP), SF-36 and SF-12 (Bergner et al., 1981; Ware and Sherbourne, 1992).

Other approaches are also possible. Physical activity level can influence many of the relevant outcomes in CFS research including cardiovascular, immune and brain system responses. As such, a valid measure of physical activity is useful to assess whether an identified abnormality is truly a phenomenon of the illness or is secondary to a sedentary lifestyle or a difference in physical activity level. The International Physical Activity

Questionnaire (IPAQ) assesses several different domains of physical activity (i.e. Job-related, Transportation, Housework, and Recreation), includes an estimate of Sitting-Time, and categorizes activities based on intensity (metabolic equivalent metric) as walking, moderate and vigorous (Craig et al., 2003).

3. Additional elements

Researchers should consider additional profiling to characterize the phenotype (or endophenotype) of CFS. These measures (shown in Table 2) may be critical for specific CFS research questions, but until demonstrated to be important in disease stratification or response to therapy, they are not currently minimum data elements.

As post-exertional malaise is a key symptom of all CFS case definitions, it would be appropriate to measure the extent of activity and how such activity might result in symptoms of fatigue and malaise. Light et al. (2009) found patients with CFS demonstrated increases after exercise that reliably exceeded responses of control subjects in mRNA for genes receptors that can detect muscle produced metabolites, genes that are essential for sympathetic nervous system processes, and immune function genes. The researchers concluded that CFS patients might have enhanced sensory signal for fatigue that is increased after exercise. Activity, or work performed is generally quantified in terms of energy used, i.e., caloric expenditure. Because this is difficult to measure during activity, total oxygen consumption which increases in a similar fashion, is typically used in its place. Sometimes represented as METs or metabolic equivalents, oxygen consumption may be assessed directly using cardiopulmonary exercise testing with measured gas exchange (Milani et al., 2006), or estimated from heart rate or other indicators of effort such as time and/or distance travelled. Assessment of effort is critical when exercise is used as a physiological stressor to elicit symptoms in CFS patients or for assessments of functional capacity as part of clinical trials. Heart rate as a percentage of age-predicted maximum is the most recognized indicator of subject effort for both maximal and submaximal exercise protocols. However, the maximal heart rate response to exercise varies widely in the general population (Balady et al., 2010) and has been shown to be blunted in some subjects with CFS (e.g., VanNess et al., 2003) and also in fibromyalgia (Ribeiro et al., 2011). As an alternative to heart rate, the peak respiratory exchange ratio (RER) is acknowledged as the most valid and reliable gauge of subject effort (Balady et al., 2010). Because it can only be obtained from ventilatory expired gas analysis, RER may not be available in all exercise studies. Similarly, submaximal exercise protocols do not provide for the measurement of peak RER. In such instances selecting alternative measures that can accurately assess effort both within and across subjects is particularly important. Cognitive impairment is a frequent and troubling symptom in CFS, and optimal objective measures are still being investigated.

Biologic measures are increasingly important in studies of CFS. Studies that include any testing need to provide details on the method of specimen collection, transport and processing, as even small deviations may introduce variation. If commercial laboratories are used, the assay method, range of normal values and lower limit of detection should be provided. In house assays need to be described. Including measures that allow calculation of allostatic load (McEwen and Stellar, 1993), along with measures of hypothalamic– pituitary-

adrenal-axis activity, sympathetic nervous system activity, immune function and allergies have all been found important as potential risk factors, or measures of illness activity (Jason et al., 2010; Klimas and Koneru, 2007; Komaroff, 2000). Molecular testing, DNA, RNA and proteomics are increasing recognized to be important in studies of CFS. There exists a substantial body of transcriptome work in CFS and significant findings have recently been published by Natelson and colleagues on the proteomics of cerebral spinal fluid in this population (Schutzer et al., 2011). There have also been early attempts at linking clinically defined sub-groups in CFS with their molecular and/or cellular phenotype (Aspler et al., 2008; Carmel et al., 2006; Kerr et al., 2008).

4. Discussion

This paper is intended to provide guidance with respect to the minimum data elements that should be reported in CFS research with the long-term goal of improving the consistency and quality of the methods used to study this complex illness. It is hoped that future CFS research will involve more interdisciplinary collaboration and interactions across various institutional settings. This would allow CFS researchers to share promising instruments, data sets, and new methods of exchanging and pooling data. For example, REDCap (research electronic data capture) is an open-access online database at http://project-redcap.org/ which allows researchers to submit their own instruments and scales, as well as use a large number already inventoried. In addition, investigators can share data across settings, thus enlarging communication lines and enhancing standardization procedures across sites. This is a free service and requires only that a given university sign up as a participating site. We believe that community researchers will increasingly utilize such websites to provide greater consensus regarding instruments and methods employed in multisite studies. However, such widespread collaborations will require thoughtful and innovative planning to properly address potential obstacles such as HIPPA and IRB concerns. One avenue that might lead to resolution of these and other challenges (e.g. intellectual property rights) involve current strategic initiatives from government funding agencies that not only encourage but also require a consortium.

Given the importance of self-report symptoms for diagnosis, below we provide more information with respect to issues of reliability and validity. For example, it is critical to develop ways of defining symptoms in a particular case definition to ensure agreement among different clinicians or researchers on whether or not a patient has met a threshold for having a particular symptom listed. The 1994 International Research case definition is recognized to have ambiguities (Reeves et al., 2003), for example it does not specify a threshold for counting the 8 core symptoms. As a consequence, some investigators use the occurrence of specific symptoms rather than severity and frequency to identify whether a person meets the threshold. In reality it is the intensity and/or duration of these somatic symptoms and not merely their presence that differentiates a person with CFS from a healthy person. Further, it is important to elicit self-report data using structured interview schedules. This ensures that questions are presented uniformly and avoids variable patient responses based on how questions are phrased. The CDC Symptom Inventory assesses information about the presence, frequency, and intensity of 19 fatigue related symptoms during the past month (Wagner et al., 2005). All eight of the critical Fukuda et al. symptoms

are included as well as 11 other symptoms (e.g. diarrhea, fever, sleeping problems, nausea etc.). Jason et al.'s (2010) DePaul Symptom Questionnaire provides another structured way to gather standardized information that can be used to aid diagnosis using the 2003 Canadian criteria (Carruthers et al., 2003) for what is termed ME/CFS. When categories lack reliability and accuracy, quality of treatment and clinical research can be significantly compromised. If CFS is to be reliably described by the clinical and scientific communities, it is imperative to deal with criterion variance issues and provide specific thresholds and scoring rules for the selected symptomatic criteria. The same issues are relevant to other aspects such as characterizing CFS disability (Jason et al., 2011b; Reeves et al., 2005; Wagner et al., 2005). In addition, instead of thresholds and a yes/no scoring of symptoms, the use of a continuous scale might address some of the issues that arise with conventional cohort stratification.

Data mining, also referred to as machine learning, might in the future help determine the types of symptoms that may be most useful in accurately describing CFS. Data mining is a technique to explore large sets of data and either (1) replicate human decisions, especially when the process by which these decisions are made are not well-understood or (2) uncover patterns in the data that would not be evident to humans because of the size and complexity of the data. In the particular case of identifying CFS symptoms, both goals are desirable; using data mining to augment physicians' diagnoses could result in more uniform diagnoses, while understanding symptoms most important in the diagnosis process could allow researchers to focus attention on the evaluation of those symptoms. Decision trees attempt to predict a classification for each patient based on successive binary choices: at each branch point of the tree, all the symptoms are examined with respect to their effect on the entropy of the diagnoses. Symptoms with high entropy are deemed important, and used to split all the cases into two parts. Successive analysis of symptoms contributing less entropy leads to further branching of the tree, until such branchings produce groupings with homogenous labels (Jason et al., 2011c). However, data mining that is "supervised" by an a priori class assignment will be wholly dependent on the original diagnostic case definition applied. In contrast, only an "unsupervised" analysis where class assignment is not provided a priori has the potential to identify patterns that support the definition of novel patient stratification strategies.

Variation in clinical diagnosis adds confusion to the field, but so do the varied etiologic categories of CFS. A plethora of viruses (e.g., viral hepatitis agents, EBV, Ross River virus, herpes viruses, entero viruses) have been postulated as either causing CFS symptoms or are associated with CFS symptoms (Hickie et al., 2006; Komaroff, 2000). Moreover, it is very likely that persistent allergies (e.g., exceptionally strong immune reactions to environmental allergens) can cause or exacerbate CFS symptoms (or be strongly associated with disease activity), so it is important to sub-categorize patients with CFS on the basis of standardized markers for all of these conditions. Even though some might consider them "exclusionary markers" for CFS, they might be variant causes of, or have strong associations with CFS and should be stated as such. This is the *paradox* of dealing with a "diagnosis of exclusion". Accordingly, accurate, standardized laboratory diagnostic tests are an essential part of the

overall diagnosis of patients with CFS. For example, before hepatitis C virus was discovered, patients were diagnosed as Non-A, Non-B hepatitis (Houghton, 2009).

The importance of sub-typing and cohort uniformity is a central theme of this paper, and there is a rich body of literature supporting the analysis of symptom constructs or patterns using statistical methodology that emerged from clinical psychology. For example, the work by Aslakson and colleagues used clinical, epidemiologic and laboratory data (Aslakson et al., 2006, 2009; Vollmer-Conna et al., 2006) to identify potential CFS sub-types.

Our current description of minimal data elements represent only a first step, and more detailed recommendations will be forthcoming specific to the different diagnostic domains. For example, in serological diagnoses, all viruses known to cause persistent or periods of reactivated viremia might be tested for through presence of the viral genome in blood and/or the presence of virus-specific antibody titers indicative of viral replication or reactivation. These might include HBV, HCV, HIV, HPV, CMV, EBV, HSV1, HSV2, HHV6a, HHV6b, HHV8, RRV as well as various enteroviruses. Circulating levels of cytokines and chemokines may be altered in some CFS patients indicative of viral replication or reactivation but it is important to determine these levels from the linear range of standard curves determined for each kine. Different species of *Borrelia* bacteria can cause Lyme disease and should be tested as well as *Coxiella burnetii*, a cause of Q fever. Severe allergies to house-hold, work-place and environmental allergies are known to be debilitating and should also be tested when possible. As indicated above, more comprehensive recommendations for relevant serological and allergy testing will be tackled in the future, as the list is long and the issues surrounding many tests will need to be addressed appropriately.

There is much work to be done in CFS research. In order for this work to be most beneficial for the patient and contribute significantly to scientific knowledge, CFS researchers need to agree on the use of standardized and valid instruments. We hope that this paper helps bring greater attention to this factor, promotes increased collaboration among investigators, and facilitates agreement upon minimum standards for reporting findings.

Additional work that needs to be done involves the collection of standardized data fully characterizing CFS patients across clinical settings will make collection of biologic samples and establishment of a biorepositories a crucial resource for the next generation of molecular testing. Having standardized data and biologic samples in the hands of experienced investigators, will increase the chance of validating findings and establishing meaningful subgroups of CFS linked to biologic alterations amenable to therapeutic interventions. At the present time, there are three groups that are attempting to do just this; one headed by the Chronic Fatigue Initiative, the other by the CFS group at the CDC, and a third by the CFIDS Association’s BioBank.

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Table 1

Minimal and additional data elements recommended.

Minimal data elements
Study design
• Type of study (e.g. case-control; case-only; cross-sectional; longitudinal)
• Recruitment method, site and time-frame
• Dates and time intervals of data collection
• Randomization protocol (when employed)
• Primary and secondary outcomes
• Language(s) used to collect data
• Statistical methods
• Ethical review
Demographics of study population
• Age, race, ethnicity, sex
• Educations, socioeconomic status
• Body mass index
• Marital status, children, living arrangements
• Employment/disability status
• Mode of onset of illness(e.g., acute, gradual; definition used to determine)
• Duration of illness
• Factors that exacerbate or trigger illness (desirable)
Case definition
• Specify case definition used for enrollment and methods used to apply definition
• Cite reference for questionnaires and scoring, or provide copies and scoring algorithm in supplementary material
Symptom inventory
• Include all case defining symptoms, frequency and severity
• Sleep
• Pain
• Include reference to questionnaire and scoring method, or provide copy in supplemental material
Medical and psychiatric exclusions and co-morbidities
• Screening laboratory tests and cut-off values for exclusion
• Exclusionary medical and psychiatric conditions - method of ascertainment
• Methods used to evaluate controls for medical/psychiatric conditions
• List of co-morbid conditions in study population
• Current medications
Self-reported functional impairment/levels of activity
• Specify instrument/questionnaire used, and method of scoring; validated options include:
– Medical Outcomes Survey Short Form-36
– Short Form-12
– Sickness Impact Profile
– International Physical Activity Questionnaire
– The Seven-Day Physical Activity Recall Questionnaire

Minimal data elements
– Time logs such as Activity Record (ACTRE) (Gerber and Furst, 1992)

Table 2

Additional Elements.

Functional Assessment
• Maximal or submaximal exercise test
• Actigraphy, pedometers
Cognition
• Cambridge Neuropsychological Test Automated Battery
Allostatic load
• Body mass index, waist/hip ratio
• Blood pressure
• Heart rate variability
• Interleukin 6 (IL-6)
• Serum Aldosterone
• 24 h urinary cortisol
Hypothalamic–Pituitary–Adrenal axis activity
• Morning or diurnal salivary cortisol curve
• ACTH
• FSH and LH (follicular or luteal phase of menstrual cycle)
• Prolactin
Immune functioning and allergies
• Natural Killer cell function
• Plasma cytokines
• Soluble mediators (cytokine receptors, Neuropeptide Y)
• EBV early antigen or IgM EBV, CMV
• IgE or skin test measures for inhalant allergens (pollen, mold, dust mites, animal dander)
Sympathetic activity
• Salivary amylase (surrogate for blood catecholamine levels)
• Heart rate variability
Coping
• Locus of control
• Beliefs towards illness
• Other coping questionnaires
Genomic and transcriptomic studies
• Genome-wide association studies (GWAS)
• Whole-genome sequencing studies (WGS)
• Transcriptional analysis (mRNA) studies
• Epigenetic studies
Proteomic studies
• Identify as possible disease-defining biomarker, disease-activity biomarker, prognostic biomarker or therapeutic biomarker
• Identify as type 0, 1 or 2 biomarker as defined in Frank and Hargreaves (2003)
• Describe methodology used (e.g. high-performance LC–MS/MS, accurate inclusion mass screening11 (AIMS), stable isotope dilution (SID)-MRM-MS (Addona et al., 2011)