Appendix I. Published Case Definition Criteria

Table I1. Published case definition criteria

| **Case Definition**  **Statements** | **General Diagnostic Criteria** | **Fatigue** | **Post-Exertional Malaise** | **Sleep** |
| --- | --- | --- | --- | --- |
| CDC, Holmes, et al., 198810 | Requires each of the following:  1. New onset of ≥6 months of persistent or relapsing, debilitating fatigue not resolved with bed rest  2. ≥8 of the symptom criteria, or 6 of the symptom criteria + ≥2 of following: low grade fever, nonexudative pharyngitis, palpable, or tender lymph nodes  3. ≥50% impairment of daily functioning as compared to premorbid levels | 6-8 of the symptoms in any category:  generalized fatigue after levels of exercise that would have been easily tolerated previously | None noted | 6-8 of the symptoms in any |
| category:  Sleep disturbance |
| Oxford  Sharpe, et al., 199146  CFS | Requires each of the following:  1. Fatigue as principal symptom  2. Definite onset of syndrome (not lifelong)  3. Syndrome must be severe, disabling have an effect on physical and mental (cognitive) functioning;  4. Present for >6 months, or >50% of the time  5. May include other symptoms: myalgias, mood and sleep disturbance | Fatigue is required to be complained  of, significantly affect the patient’s functioning, be disproportionate to exertion, represent a clear change from a previous state and be present >50% of the time. | None noted | Sleep disturbances are required to be complained of, not a response to external disturbances, changes from previous states, and persistent. |
| London  Dowsett, et al., 199447  ME/CFS | Must meet all 3 criteria:  1. Exercise-induced fatigue, see fatigue criteria.  2. Impairment of short-term memory and loss of powers of concentration, usually coupled with other neurological and psychological disturbances, see neuroglogic/cognitive criteria.  3. Fluctuation of symptoms, usually precipitated by either physical or mental exercise. | Exercise-induced fatigue precipitated by trivially small exertion (physical or mental) relative to the patient’s previous exercise tolerance. | Nothing noted | Nothing noted |

Table I1. Published case definition criteria (continued)

| **Case Definition**  **Statements** | **Pain** | **Neurological/cognitive** |
| --- | --- | --- |
| CDC, Holmes, et al., 198810 | 6-8 of the symptoms in any category:  Myalgia  Migratory arthralgia without joint swelling or redness  Painful lymph notes  Muscle discomfort | 6-8 of the symptoms in any category:  Neuropsychological complaints  Prolonged (>24 hours) generalized headaches |
| Oxford  Sharpe, et al., 199146  CFS | Myalgia should be complained of, disproportionate to exertion, a change  from a previous state, persistent or recurrent, and should be distinguished from joint pain or weakness. | Mood disturbances should be complained of, significant changes from  previous state and should be relatively persistent or recurrent. This may include depression, loss of interest or pleasure, anxiety, emotional liability or irritability. |
| London  Dowsett, et al., 199447  ME/CFS | Nothing noted | Impairment of short-term memory and loss of powers of concentration, usually coupled with other neurological and psychological disturbances such as emotional lability (being upset by things that would not normally cause distress), nominal dysphasia (difficulty finding the right word), disturbed sleep patterns, dysequilibrium (imbalance or unsteadiness rather than vertigo/spinning round) or tinnitus (noises in the ear). |

Table I1. Published case definition criteria (continued)

| **Case Definition**  **Statements** | **Other Criteria** | **Additional Considerations** |
| --- | --- | --- |
| CDC, Holmes, et al., 198810 | 6-8 of the symptoms in any category:  Mild fever, sore throat, or description of the main symptom complex as initially developing over a few hours to a few days | None |
| Oxford  Sharpe, et al., 199146  CFS | Disability refers to any restriction or lack of ability to perform an activity within the range considered normal for a human being, it should be distinguished from impairment of function and handicap. | None |
| London  Dowsett, et al., 199447  ME/CFS | Fluctuation of symptoms, usually precipitated by either physical or mental exercise. | None |

Table I1. Published case definition criteria (continued)

| **Case Definition**  **Statements** | **General Diagnostic Criteria** | **Fatigue** | **Post-Exertional Malaise** | **Sleep** |
| --- | --- | --- | --- | --- |
| CDC ≥6 months  Fukuda, et al., 19944  CFS | 2 of the fatigue criteria and  ≥4 of the criteria in any category | Unexplained, persistent fatigue ≥6 months not due to ongoing exertion, not substantially relieved by rest, of new onset, and results in a significant reduction in previous activity levels. | Post-exertional malaise | Unrefreshing sleep |
| Canadian ≥ 6 months  Carruthers, et al., 20032  ME/CFS | All of the following:  Fatigue  Post-exertional fatigue  Sleep dysfunction  Pain  ≥2 of the following:  Neurological/cognitive manifestations  ≥1 symptoms from ≥2 of the following categories: Autonomic Neuroendocrine Immune | New onset, unexplained, persistent, or  recurrent physical and mental fatigue that substantially reduces activity level. | Loss of physical and mental stamina, rapid muscular and cognitive fatigability, post- exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient’s cluster of symptoms to worsen. There is a slow recovery period, usually ≥24 hours. | Unrefreshed sleep or sleep quantity or rhythm disturbances such as reversed or chaotic diurnal sleep rhythms.\* |

Table I1. Published case definition criteria (continued)

| **Case Definition**  **Statements** | **Pain** | **Neurological/cognitive** |
| --- | --- | --- |
| CDC ≥6 months  Fukuda, et al., 19944  CFS | Muscle pain  Multi-joint pain without swelling or redness  Headaches of new type or severity  Recurrent sore throat  Tender cervical or axillary lymph nodes | Impaired memory of concentration |
| Canadian ≥ 6 months  Carruthers, et al., 20032  ME/CFS | Significant myalgia and/or arthralgia, is often widespread and migratory in nature. Often there are significant headaches of new type, pattern or severity.\*\* | ≥2 of the following:  Confusion, impaired concentration and short-term memory, disorientation, difficulty with information processing, categorizing and word retrieval, and perceptual and sensory disturbances (e.g., spatial instability and disorientation and inability to focus vision). Ataxia, muscle weakness and fasciculations are common.  There may be overload phenomena: cognitive, sensory (e.g., photophobia and hypersensitivity to noise); and/or emotional overload, which may lead to crash periods and/or anxiety. |

Table I1. Published case definition criteria (continued)

| **Case Definition**  **Statements** | **Other Criteria** | **Additional Considerations** |
| --- | --- | --- |
| CDC ≥6 months  Fukuda, et al., 19944  CFS | Recurrent sore throat  Tender cervical or axillary lymph nodes | Diagnosis of CFS-like illness if ≥6 months  fatigue but doesn’t meet other criteria |
| Canadian ≥ 6  months  Carruthers, et al., 20032  ME/CFS | ≥1 symptoms from ≥2 of the following categories:  1. Autonomic manifestations: orthostatic hypotension, neurally mediated, postural orthostatic tachycardia syndrome, delayed postural hypotension; light-headedness; extreme pallor; nausea and irritable bowel syndrome; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmias; exertional dyspnea.  2. Neuroendocrine manifestations: loss of thermostatic stability. subnormal body temperature and marked diurnal fluctuation, sweating episodes, recurrent feelings of feverishness and cold extremities; intolerance of extremes of heat and cold; marked weight change. anorexia or abnormal appetite; loss of adaptability and worsening of symptoms with stress.  3. Immune manifestations: tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms, general malaise, new sensitivities to food, medications and/or chemicals. | \*There is a small number of patients who  have no pain or sleep dysfunction, but no other diagnosis fits except ME/CFS. A diagnosis of ME/CFS can be entertained when this group has an infectious illness type onset.  \*\*Some patients have been unhealthy for other reasons prior to the onset of ME/CFS and lack detectable triggers at onset and/or have more gradual or insidious onset. |

Table I1. Published case definition criteria (continued)

| **Case Definition**  **Statements** | **General Diagnostic Criteria** | **Fatigue** | **Post-Exertional Malaise** | **Sleep** |
| --- | --- | --- | --- | --- |
| Reeves, et al.,  200549  CFS | Follows Fukuda, 1994 criteria, meant to  define how to apply criteria | Fatigue (must satisfy all):  - Lasting >6 months  - Not relieved by rest (by answering “a little or not at all” to the question “is your fatigue relieved by rest?)  - Causing substantial reduction in occupational, educational, social, or recreational activities (by answering “a lot” to “Does fatigue interfere with…”) Severe fatigue as >medians of the MFI-20 general fatigue (>13) or reduced activity (>10) scales. | Nothing noted | Nothing noted |
| Revised Canadian  ≥6 months  Jason, et al.,  201048  ME/CFS | All of the following :  ≥ 6 months of persistent fatigue  Post-exertional malaise and/or post- exertional fatigue  Unrefreshing sleep or disturbance of sleep quantity or rhythm disturbance  ≥1 of myofascial and/or joint pain  ≥2 neurological/cognitive manifestations  ≥1 symptom from 2 of the following 3 categories:  1. Autonomic manifestations,  2. Neuroendocrine manifestations  3. Immune manifestation | ≥6 months, persistent or recurring chronic fatigue that is not lifelong and results in substantial reductions in previous levels of occupational, educational, social, and personal activities. | Post-exertional malaise and/ or post-exertional fatigue. With activity there must be a loss of physical or mental stamina, rapid/sudden muscle or cognitive fatigability, post-exertional malaise and/or fatigue and a tendency for other associated symptoms within the patient’s cluster of symptoms to worsen. The recovery is slow, often taking 2-24 hours or longer. | Unrefreshing sleep or disturbance of sleep quantity or rhythm disturbance. May include unrefreshing sleep, prolonged sleep (including frequent naps), disturbed sleep (e.g., inability to fall asleep or early awakening) and/or day/night reversal. |

Table I1. Published case definition criteria (continued)

| **Case Definition**  **Statements** | **Pain** | **Neurological/cognitive** |
| --- | --- | --- |
| Reeves, et al., 200549  CFS | Nothing noted | Nothing noted |
| Revised Canadian ≥6 months  Jason, et al., 201048  ME/CFS | Pain (or discomfort) that is often widespread and migratory in nature.  ≥1 symptom from any of the following:  Myofascial and/or joint pain, myofascial pain can include deep pain, abdomen/stomach pain, or achy and sore muscles.  Pain, stiffness, or tenderness may occur in any joint but must be present in  ≥1 joint and lacking edema or other signs of inflammation. Abdominal and/or head pain. May experience stomach pain or chest pain. Headaches often described as localized behind the eyes or in the back of the head. May include headaches localized elsewhere, including migraines. Headaches would need to be more frequent than they were before, which would indicate new pattern, of a new type as compared to headaches previously experienced, or different in severity type as compared to headaches previously experienced by the patient. | ≥2 neurological/cognitive manifestations:  Impaired memory (self-reported or observable disturbance in ability to recall information or events on a short-term basis); difficulty focusing vision and attention (disturbed concentration may impair ability to remain on task, to screen out extraneous/excessive stimuli); loss of depth perception; difficulty finding the right word; frequently forget what wanted to say; absent mindedness; slowness of thought; difficulty recalling information; need to focus on one thing at a time; trouble expressing thought; difficulty comprehending information; frequently lose train of thought; sensitivity to bright lights or noise; muscle weakness/muscle twitches |

Table I1. Published case definition criteria (continued)

| **Case Definition**  **Statements** | **Other Criteria** | **Additional Considerations** |
| --- | --- | --- |
| Reeves, et al.,  200549  CFS | -Presence of 4 of 8 case-defining symptoms (by answering “all of the time or most of the time” to questions about symptoms, e.g. “during the past month how often have you had a sore throat?)”  -Functional impairment defined as score <25th percentile of the SF-36 on the physical function (<70), or role physical (<50), or social function (<75), or role emotional (<66.7)  -Reporting >4 symptoms and scoring >25 on the Symptom Inventory Case Definition Subscale | None |
| Revised Canadian  ≥6 months  Jason, et al., 201048  ME/CFS | ≥1 symptom from 2 of the following 3 categories:  1. Autonomic manifestations: neurally mediated hypotension, postural orthostatic tachycardia, delayed postural hypotension, palpitations with or without cardiac arrhythmias, dizziness or fainting, feeling unsteady on the feet--disturbed balance, shortness of breath, nausea, bladder dysfunction, or irritable bowel syndrome.  2. Neuroendocrine manifestations recurrent feelings of feverishness and cold extremities, subnormal body temperature and marked diurnal fluctuations, sweating episodes, intolerance of extremes of heat and cold, marked weight change-loss of appetite or abnormal appetite.  3. Immune manifestations: recurrent flu-like symptoms, non-exudative sore or scratchy throat, repeated fevers and sweats, lymph nodes tender to palpitation--generally minimal swelling noted, new sensitivities to food, odors, or chemicals. | None |

Table I1. Published case definition criteria (continued)

| **Case Definition**  **Statements** | **General Diagnostic Criteria** | **Fatigue** | **Post-Exertional Malaise** | **Sleep** |
| --- | --- | --- | --- | --- |
| International Consensus Statement Carruthers, et al., 20113  ME | A. Post-exertional neuroimmune exhaustion:  cardinal  B. Neurological impairments ≥ 1 from 3 of the 4 symptom categories:  1. Neurocognitive impairments  2. Pain  3. Sleep disturbance  4. Neurosensory, perceptual, and motor disturbances  C. Immune, gastrointestinal, and genitourinary impairments  ≥1 symptom from ≥3 of the following:  1.Flu-like symptoms  2. Susceptibility to viral infections  3.Gastrointestinal symptoms  4.Gentourinary symptoms  5. Sensitivities to food, medications, odors or chemicals  D. Energy production⁄transportation impairments: ≥1  1. Cardiovascular – orthostatic, etc.  2. Respiratory – shortness of breath, etc.  3. Thermostatic instability  4. Temperature intolerance | ≥1 Symptom:  1. Cardiovascular: e.g. inability to tolerate an upright position - orthostatic intolerance, neurally mediated hypotension, postural orthostatic Tachycardia syndrome, palpitations with or without cardiac arrhythmias, light-headedness⁄dizziness  2. Respiratory: e.g. air hunger, labored breathing, fatigue of chest wall muscles  3. Loss of thermostatic stability: e.g. subnormal body temperature, marked diurnal fluctuations; sweating episodes, recurrent feelings of feverishness with or without low grade fever, cold extremities  4. Intolerance of extremes of temperature | 1. Marked, rapid physical and⁄or cognitive fatigability in response to exertion, which may be minimal such as activities of daily living or simple mental tasks, can be debilitating and cause a relapse  2. Post-exertional symptom exacerbation: e.g. acute flu-like symptoms, pain and worsening of other symptoms.  3. Post-exertional exhaustion may occur immediately after activity or be delayed by hours or days.  4. Recovery period is prolonged, usually taking 24 hour longer. A relapse can last days, weeks or longer.  5. Low threshold of physical and mental fatigability (lack of stamina) results in a substantial reduction in pre-illness activity level. | ≥1 from Sleep, Pain, or Neurological/cognitive Categories:  Disturbed sleep patterns: e.g. insomnia, prolonged sleep including naps, sleeping most of the day and being awake most of the night, frequent awakenings, awaking much earlier than before illness onset, vivid dreams⁄nightmares  b. Unrefreshed sleep: e.g. awaken feeling exhausted regardless of duration of sleep, day-time sleepiness |

Table I1. Published case definition criteria (continued)

| **Case Definition**  **Statements** | **Pain** | **Neurological/cognitive** |
| --- | --- | --- |
| International Consensus Statement Carruthers, et al., 20113  ME | ≥1 from Sleep, Pain, or Neurological/cognitive categories:  Headaches: e.g. chronic, generalized headaches often involve aching of the eyes, behind the eyes or back of the head that may be associated with cervical muscle tension; migraine; tension headaches  b. Significant pain can be experienced in muscles, muscle-tendon junctions, joints, abdomen or chest. It is non-inflammatory in nature and often migrates. e.g. generalized hyperalgesia, widespread pain (may meet fibromyalgia criteria), myofascial or radiating pain | ≥1 from Sleep, Pain, or Neurological/cognitive categories:  1. Neurocognitive impairments:  a. Difficulty processing information: slowed thought, impaired concentration e.g. confusion, disorientation, cognitive overload, difficulty with making decisions, slowed speech, acquired or exertional dyslexia  b. Short-term memory loss: e.g. difficulty remembering what one wanted to say, what one was saying, retrieving words, recalling information,  poor working memory  2. Neurosensory, perceptual and motor disturbances  a. Neurosensory and perceptual: e.g. inability to focus vision, sensitivity to light, noise, vibration, odor, taste and touch; impaired depth perception  b. Motor: e.g. muscle weakness, twitching, poor coordination, feeling unsteady on feet, ataxia |

Table I1. Published case definition criteria (continued)

| **Case Definition**  **Statements** | **Other Criteria** | **Additional Considerations** |
| --- | --- | --- |
| International Consensus Statement Carruthers, et al., 20113  ME | Immune, gastrointestinal and genitourinary impairments; ≥1 symptom from ≥3 of the following:  1. Flu-like symptoms typically worsen with exertion e.g. sore throat, sinusitis, cervical and ⁄ or axillary  lymph nodes may enlarge or be tender on palpitation  2. Susceptibility to viral infections with prolonged recovery periods  3. Gastro-intestinal tract: e.g. nausea, abdominal pain, bloating, irritable bowel syndrome  4. Genitourinary: e.g. urinary urgency or frequency, nocturia  5. Sensitivities to food, medications, odors or chemicals | None |

**Abbreviations:** CDC= Centers for Disease control and Prevention; CFS= chronic fatigue syndrome; e.g.= example; etc.= etcetera; ME= myaligic encephalomyelitis; MFI-20=Multidimensional Fatigue Inventory, 20-item; SF-36= 36-item Short Form Survey.