

## **European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE)**

### **COST action CA15111**

#### **Deliverable 10**

##### **Common consensus protocol for economic loss calculation due to ME/CFS**

### **1 Introduction**

#### **1.1 ME/CFS**

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a poorly understood, serious, complex, multi-system disorder, characterized by symptoms lasting at least six months, with severe incapacitating fatigue not alleviated by rest, and other symptoms, many autonomic or cognitive in nature, including profound fatigue, cognitive dysfunction, sleep disturbances, muscle pain, post-exertional malaise, which lead to substantial reductions in functional activity and quality of life [1,2,3]. Symptomatology, severity and disease progression are extremely variable. It most commonly occurs between the ages of 20 to 50, but affects all age groups. Some three quarters of patients are female [7,8,9]. There is no Europe-wide prevalence data, but if the commonly held belief that there are some 250,000 sufferers in the UK is correct, then there may be some two million patients in Europe as a whole.

#### **1.2 EUROMENE**

The EUROMENE network was established to enable a collaborative, Europe-wide approach to address serious gaps in knowledge of ME/CFS. Its working groups focus on epidemiology, biomarkers and diagnostic criteria, clinical research, and socio-economics, the latter being the remit of Working Group 3. The network now has representation from twenty-two countries, and all the working groups have active involvement of researchers from across Europe.

#### **1.3 Working Group 3 (socio-economics)**

The objective of Working Group 3 (socio-economics) is to coordinate efforts to determine the social impact of ME/CFS and to appraise the economic damage from the disease, and to do so by enabling the estimation of the burden of ME/CFS to society and the provision of long-term trend estimates for societal impact. The specific tasks for which the working group has responsibility are:-

1. To survey European countries existing data on economic loss due to ME/CFS;
2. To develop approaches to calculate direct economic loss due to ME/CFS;
3. To develop approaches to calculate indirect economic burden due to ME/CFS;
4. To provide integrated outcome assessment framework.

A step towards achieving these objectives is the current deliverable, which is the creation of a Common consensus protocol for economic loss calculation due to ME/CFS.

- 1.4 Subsequent sections of this report consider the problems to be addressed, including that of case definitions, the role of cost-of-illness studies, the data required, both to assess conformity to case definitions and to measure costs, which health questionnaire to use to assess levels of incapacity, and finally the central role of Purchasing Power Parities in making valid comparisons between countries and in enabling collation of data at a European level.

## 2 Problems to be addressed

- 2.1 The previous deliverable for Working Group 3 identified, and discussed in detail, a number of problems requiring resolution [7]. In summary, these were:-

- Lack of agreement over case definition.
- Unwillingness of a high proportion of doctors to recognise or diagnose the disease.
- As a result, lack of knowledge of incidence and prevalence of the disease.

## 3 Case Definitions

- 3.1 A major problem in determining the overall burden of disease attributable to ME/CFS arises from the fact that there has been little agreement over case definition. Brurberg et al [8], for example, have listed twenty case definitions developed from 1988 onwards, which tend to define different populations and which therefore impact significantly on the perceived prevalence of the disease, and also levels of severity and hence of need for care within the identified patient population.
- 3.2 In recent years, the case definition most commonly used for research purposes has been that produced by the US Centers for Disease Control in 1994, otherwise known as the Fukuda definition [9]. More recently still, the Canadian Consensus Criteria (CCC) have been widely accepted [10], and identify a more severely affected group of patients than the Fukuda definition. A UK study found that almost exactly half of the patients identified by Fukuda were identified by the CCC [11]. A parallel study in the UK concluded that there were advantages to using both definitions, in order to take advantage of the greater sensitivity of the Fukuda definition, and the greater specificity of the CCC [12]. Working Group 1 of EUROMENE (Epidemiology) endorsed this approach [13], and proposes that these two definitions should be used in all participating European countries.
- 3.3 Working Group 3 (Socio-economics) accepts this guidance, and recommends use of a symptom checklist enabling data to be collected of such a nature that mapping algorithms can be applied to them enabling conformity to both Fukuda and CCC to be determined. An example symptom checklist is presented in Table 1 below:-

**Table 1**

### Symptom Checklist

	Yes/No
Debilitating fatigue not relieved by bed rest	
Chronic persisting or relapsing fatigue	
Severe disabling fatigue affecting physical and mental functioning	
Infection at onset or presentation corroborated by laboratory evidence	
6 months minimum duration of fatigue or illness	

Substantial functional impairment	
50% decrease in activity	
Significant disruption of usual activities	
Functional impairment that can be described as disabling	
Presence of cognitive or neuropsychiatric symptoms	
Mental fatigue	
Photophobia	
Transient visual scotomata	
Forgetfulness	
Excessive irritability	
Confusion	
Difficulty thinking	
Inability to concentrate	
Depression	
Substantial impairment in short-term memory or concentration	
Sore throat	
Painful cervical or axillary lymph nodes	
Swollen lymph nodes	
Muscle discomfort	
Myalgia	
Migratory arthralgia without joint swelling or redness	
Multi-joint pain without swelling or redness	
Generalised headaches (of a type, severity, or pattern that is different from headaches the patient may have had in the premorbid state)	
Sleep disturbance (hypersomnia or insomnia or unrefreshing sleep)	
Prolonged (24 hours or greater) generalised fatigue from levels of exercise that would have been easily tolerated in the patient's premorbid state	
Post-exertional malaise lasting more than 24 hours	
Mild fever or chills	
Unexplained generalized muscle weakness	
Description of the main symptom complex as initially developing over a few hours to a few days	
Mood disturbance	
Perceptual or sensory disturbances	
Hypersensitivity to noise	
Ataxia	
Orthostatic intolerance or other autonomic manifestation	
Loss of thermostatic ability or other neuroendocrine manifestation	
Intolerance of extremes of heat and cold	
New sensitivities to food, medications and/or chemicals	
New onset of short term memory impairment	
Duration of illness is at least 6 months	
Definite evidence of infection at onset or presentation corroborated by laboratory evidence	
<b>Other Diseases:</b>	
Anaemia	
Addison's disease	
Cushing's Syndrome	
Hyperthyroidism	
Hypothyroidism	
Hashimoto's Disease	
Diabetes mellitus	
Cancer	
Upper airway resistance syndrome	
Obstructive or central sleep apnea	
Iron overload syndrome	
Rheumatological disorders e.g. rheumatoid arthritis, polymyositis	
Chronic or subacute bacterial e.g. endocarditis, TB, Lyme disease	
Fungal disease e.g. histoplasmosis or coccidioidomycosis	
Parasitic disease e.g. toxoplasmosis or other helminthic infestation	
Other infectious diseases e.g. HIV infection, chronic hepatitis	

Neurological disorders e.g. multiple sclerosis (MS), Parkinsonism, Myasthenia gravis	
Vitamin B12 deficiency	
Anxiety disorder	
Depressive disorder including endogenous depression	
Bipolar disorder	
Schizophrenia	
Substance abuse	
Melancholic (severe, major) or psychotic depression	
Eating disorder	
Dementia	
Delusional disorders	
Psychosis	
Organic brain disease	
Hyperventilation syndrome	
Fibromyalgia Syndrome (FMS)	
Myofascial Pain Syndrome (MPS)	
Temporomandibular Joint Syndrome (TMJ),	
Interstitial Cystitis	
Irritable Bladder Syndrome	
Irritable Bowel Syndrome	
Raynaud's Phenomenon	
Migraine	
Sicca Syndrome	
Premenstrual Syndrome	
Multiple Chemical Sensitivity	

Source: Osoba et al (2007) [14]

#### 4 Cost-of-illness studies

4.1 The overall economic burden of ME/CFS within participating European countries could be determined by the implementation of cost-of-illness studies. These would have to be prevalence rather than incidence based [15], because little is known about the prognosis of the disease. There have been Europe-wide cost-of-illness studies in other conditions, such as cancer [16], and the output from such studies can be invaluable, both in informing health and social care policy, and facilitating the management of health and care services. Tarricone wrote: "COI can provide information to support the political process as well as the management functions at different levels of the healthcare organisations. To do that, the design of the study must be innovative, capable of measuring the true cost to society; to estimate the main cost components and their incidence over total costs; to envisage the different subjects who bear the costs; to identify the actual clinical management of illness; and to explain cost variability." [17]

#### 4.2 Data items required for cost-of-illness studies

In order to carry out a cost-of-illness study, there is a need for comprehensive data collection at the level of the individual patient. One example of the range and scope of such data is given in table 2 below. This comes from a Korean source [18], and it must be borne in mind that there may be variations in the availability of some data items due to differences between countries in the organisation and funding of health care.

**Table 2**

**Examples of costs associated with health outcomes**

Direct health care costs		Direct non-health care costs	Indirect costs
<ul style="list-style-type: none"> <li>- Institutional inpatient care</li> <li>Hospitalization specialized unit (ICU, CCU)</li> <li>Nursing home</li> <li>Terminal care or Hospice</li> <li>- Institutional outpatient service</li> <li>Clinic and ER</li> <li>- Home health care</li> <li>- Physician services</li> <li>General practitioner (GPs)</li> <li>Specialists</li> <li>- Ancillary services</li> <li>Nurses (RNs, Nursing Aid)</li> <li>Nutritionists</li> <li>Physical therapist</li> <li>Ambulance</li> <li>- Overhead allocated to technology</li> <li>Fixed costs of utilities</li> <li>Space and storage</li> <li>Support services</li> <li>Capital costs (depreciation)</li> <li>Construction of facilities</li> <li>Relocation expenses</li> <li>Device or equipment cost</li> <li>- Variable costs of utilities</li> <li>- Medications (prescription and non-prescription)</li> <li>Drug costs</li> <li>Training in new procedures</li> <li>Dispensing and administration</li> <li>Monitoring</li> </ul>	<ul style="list-style-type: none"> <li>- Devices and applications</li> <li>- Drugs, supplies, devices provided by household</li> <li>- Diagnostic test</li> <li>Imaging</li> <li>Laboratory testing</li> <li>- Treatment services</li> <li>Surgery</li> <li>Consumable supplies, personnel time, equipment</li> <li>Treatment of complications</li> <li>Blood products</li> <li>Oxygen</li> <li>Radiation therapy</li> <li>Special diets</li> <li>- Prevention services</li> <li>Screening space</li> <li>Vaccination, prophylaxis</li> <li>Disease prevention in contacts of known cases</li> <li>- Rehabilitation</li> <li>- Training and education</li> <li>Health education</li> <li>Self-care training for patients</li> <li>Life-support skills for general population</li> </ul>	<ul style="list-style-type: none"> <li>- Social services</li> <li>Counseling</li> <li>Retraining</li> <li>- Program evaluation</li> <li>Monitoring impact of program or technology</li> <li>Data analysis</li> <li>- Repair of property destruction</li> <li>- Legal costs</li> <li>- Transportation costs</li> <li>- Time (searching, travelling, waiting etc.)</li> <li>- Childcare or Housekeeping</li> </ul>	<ul style="list-style-type: none"> <li>- Productivity losses</li> <li>Morbidity</li> <li>Mortality</li> <li>Impairment</li> <li>Job absenteeism</li> <li>- Foregone leisure time</li> <li>- Time spent by family &amp; visitors attending patient</li> </ul>

*Source : Jo C, 2014*

4.3 It will be appreciated that this list involves a combination of system costs and costs to the individual with ME/CFS and those close to him or her. A study has been undertaken in Italy to determine costs to the individual [19]. This assessing the direct and indirect costs of ME/CFS via a questionnaire distributed via Italian patient associations. By estimating the cost of medical procedures and the cost of lost working time, the study arrived at an estimate for the total economic burden of the disease in the region. The questionnaire was discussed in detail; its specificity and applicability to different countries. This study could, the Working Group felt, be repeated in other countries, in order to enable the acquisition of data capable of direct comparison between countries. The study aimed to relate the cost impact on people with ME/CFS to their clinical condition and the severity of the disease through the use of the EuroQol-5D instrument to assess clinical state. A version of EuroQol-5D is attached for information (Table 3).

**Table 3**

**EuroQol-5D-5L: Health Questionnaire-English version for the UK**

<p>Under each heading, please tick the ONE box that best describes your health TODAY.</p> <p><b>MOBILITY</b> I have no problems in walking about <input type="checkbox"/> I have slight problems in walking about <input type="checkbox"/> I have moderate problems in walking about <input type="checkbox"/> I have severe problems in walking about <input type="checkbox"/> I am unable to walk about <input type="checkbox"/></p> <p><b>SELF-CARE</b> I have no problems washing or dressing myself <input type="checkbox"/> I have slight problems washing or dressing myself <input type="checkbox"/> I have moderate problems washing or dressing myself <input type="checkbox"/> I have severe problems washing or dressing myself <input type="checkbox"/> I am unable to wash or dress myself <input type="checkbox"/></p> <p><b>USUAL ACTIVITIES</b> (<i>e.g. work, study, housework, family or leisure activities</i>) I have no problems doing my usual activities <input type="checkbox"/> I have slight problems doing my usual activities <input type="checkbox"/> I have moderate problems doing my usual activities <input type="checkbox"/> I have severe problems doing my usual activities <input type="checkbox"/> I am unable to do my usual activities <input type="checkbox"/></p> <p><b>PAIN / DISCOMFORT</b> I have no pain or discomfort <input type="checkbox"/> I have slight pain or discomfort <input type="checkbox"/> I have moderate pain or discomfort <input type="checkbox"/> I have severe pain or discomfort <input type="checkbox"/> I have extreme pain or discomfort <input type="checkbox"/></p> <p><b>ANXIETY / DEPRESSION</b> I am not anxious or depressed <input type="checkbox"/> I am slightly anxious or depressed <input type="checkbox"/> I am moderately anxious or depressed <input type="checkbox"/> I am severely anxious or depressed <input type="checkbox"/> I am extremely anxious or depressed <input type="checkbox"/></p> <p>We would like to know how good or bad your health is TODAY, on a scale numbered from 0 to 100. 100 means the best health you can imagine. 0 means the worst health you can imagine. Mark an X on the scale to indicate how your health is TODAY.</p>
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**5. Europe-wide information**

5.1 A comprehensive review of the financing and organisation of health care in the European Union, conducted by WHO for the European Observatory on Health Systems and Policies in 2009, documented in detail the diversity of such arrangements throughout Europe [20]. Similar diversity is found in terms of health outcomes and general levels of health, but there is no correlation between accessibility of health care and funding levels. [21].

5.2 Making valid international comparisons

There is a problem making valid comparisons of health care costs between countries which differ markedly in terms of wealth and levels of economic development. We propose that, for ME/CFS, Purchasing Power Parity (PPP) should be used. This is a method for comparing

the price of goods between countries. Using a “basket of goods”, things that are commonly bought by consumers, such as bread, milk, shampoo, the PPP is a ratio of the total cost of these goods between two countries. In this way one can compare what 1 unit of currency can buy across different countries, and convert the values back to a single reference currency [22]. For Europe, the obvious choice for the reference currency is the Euro.

## **6 Summary of Recommendations**

- 6.1. To facilitate international comparisons of the economic impact of ME/CFS, we recommend Europe-wide adoption of the Fukuda (CDC-1994) case definition alongside the Canadian Consensus Criteria CCC (paragraph 3.1).
- 6.2. We recommend the pan-European use of a common symptom checklist, capable of being mapped by computerised algorithms onto both the Fukuda case definition and the CCC.
- 6.3. Prevalence based cost-of-illness studies, based on these case definitions, should be carried out in different countries, to determine the overall cost burden attributable to ME/CFS (paragraph 4.1).
- 6.4. A list of data items required for cost-of-illness studies has been identified. Individual participating countries should examine this, to ensure that, insofar as these are derivable from routine data collection, that systems are in place to ensure that they are collected.
- 6.5. The availability in participating countries of the relevant data items referred to above which are required for cost-of illness studies should be examined, with a view to achieving convergence, and facilitating international comparisons (paragraph 4.2).
- 6.6. The EuroQol-5D instrument should be used to determine the relationship if any between disease severity and economic impacts, as in the Italian study reported in this document. We further recommend that the Italian study be replicated in other countries, to enable international comparisons to be made,
- 6.7. Given the diversity of patterns of health care organisations and funding health, as well as of outcomes and general levels of health, as well as of national wealth and levels of economic development, we recommend the use of Purchasing Power Parities (PPP) in order both to make valid international comparisons and to collate meaningful statistics at a European level (paragraph 5.1).

## **References**

1. Lindan R. Benign Myalgic Encephalomyelitis. *Can Med Assoc J* (1956); 75(7): 596-7.
2. Acheson ED. The clinical syndrome variously called myalgic encephalomyelitis, Iceland disease and epidemic neuromyasthenis. *Am. Med.* (1959); 26(4): 589-595.
3. Carruthers BM, Jain AK, De Meirleir KL, et al. Myalgic encephalomyelitis/chronic fatigue syndrome : Clinical working case definition, diagnostic and treatment protocols. *Journal of Chronic Fatigue Syndrome* (2003); 11(1): 7-116.
4. Johnstone SC, Staines DR, Marshall-Gradisnik SM. Epidemiological characteristics of chronic fatigue syndrome/myalgic encephalomyelitis in Australian patients. *Clinical Epidemiology* (2016); 8: 97-107.

5. Pheby D, Lacerda E, Nacul L, et al. A disease register for ME/CFS: Report of a pilot study. *BMC Research Notes* (2011); 4: 139-146.
6. Lloyd AR, Hickie I, Boughton CR, et al. Prevalence of chronic fatigue syndrome in an Australian population. *Med. J. Aust.* (1990); 153(9): 522-8.
7. Cost Action 15111 (EUROMENE) - Working Group 3: Socio-Economics. Deliverable 15 Summary of evaluated socio-economic impact and direct and indirect costs caused by ME/CFS in Europe). April 2018.
8. Brurberg KG, Fønhus MS, Larun L, et al. *BMJ Open* 2014;4:e003973. doi:10.1136/bmjopen-2013-003973.
9. Fukuda K, Strauss SE, Hickie I et al, for the International Chronic Fatigue Syndrome Study Group. The Chronic Fatigue Syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* (1994); 121(12):953-959.
10. Carruthers BM, Jain AK, De Meirleir KL et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Guidelines - A Consensus Document. *Journal of Chronic Fatigue Syndrome* 2003, 11(1):7-115.
11. Pheby D, Lacerda E, Nacul L, et al. A Disease Register for ME/CFS: Report of a Pilot Study. *BMC Research Notes* (2011); 4:139.
12. Nacul LC, Lacerda EM, Pheby D, Campion P, Molokhia M, Fayyaz S, Drachler M, Poland F, A Howe A, Leite JC. Prevalence and incidence of myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care. *BMC Medicine* (2011); 9: 91.
13. European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE) - COST action CA15111, Working Group 1 (Epidemiology). Deliverable 7: Joint publication manuscript on ME/CFS European practices in diagnosis and treatment based on survey data (2017).
14. Osoba T, Pheby D, Gray S, Nacul L. The Development of an Epidemiological Definition for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Journal of Chronic Fatigue Syndrome* (2007); 14(4): 61-84.
15. Byford S, Torgerson DJ, Raftery J. Cost of illness studies. *BMJ*; 320: 1335 (13<sup>th</sup> May 2000)
16. Luengo-Fernandez R, Leal J, Gray A, Sullivan. Economic burden of cancer across the European Union: a population-based cost analysis. *Lancet Oncol* (2013); 14: 1165–74
17. Tarricone R. Cost-of-illness analysis: What room in health economics? *Health Policy* (2006); 77: 51–63
18. Jo C. Cost of illness studies: concepts, scopes and methods. <http://dx.doi.org/10.3350/cmh.2014.20.4.327> Accessed 30<sup>th</sup> September 2018.
19. Brenna E, Gitto L. Sindrome de affaticamento cronico: una prima analisi empirica per l'Italia. *Politiche Sanitarie* (2018); 18(1): 1-9.
20. Thomson S, Foubister T, Mossialos E. Financing health care in the European Union: Challenges and policy responses. WHO (for the European Observatory on Health Systems and Policies), 2009.
21. Björnberg A. Euro Health Consumer Index 2017: Report. Health Consumer Powerhouse, 2018
22. Eurostat/OECD. *Eurostat/OECD Methodological Manual on Purchasing Power Parities*. Luxembourg. Publications Office of the European Union, 2012.