EUROPEAN COOPERATION
IN SCIENCE AND TECHNOLOGY

European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

COST action CA15111

Minutes of the 29 September 2016 Core Group meeting:

Participants:
Chair: Modra Murovska (Latvia)
Co-chair: Eliana Lacerda (United Kingdom)
GH member - Uldis Berķis (Latvia)
WG1 leader - Jesus Castro-Marrero (Spain)
WG2 leader - Carmen Scheibenbogen (Germany)
WG3 leader - Derek Pheby (UK)
WG4 leader - Elin Bolle Strand (Norway)
WG5 leader - Evelina Shikova-Lekova (Bulgaria)
WG6 leader - Lorenzo Lorusso (Italy)

1. Welcome - Modra Murovska, COST chair

2. Reports of the WG leaders on the present achievements, identified problems and ways to overcome:

WG1 - Few studies estimating incidence of ME/CFS in Europe were published so far. While Nacul at all found "*overall estimated minimal yearly incidence was 0.015%*" for the UK population [4]; Bakken et all, found "*overall incidence rate was 25.8 per 100,000 person years (95% confidence interval (CI): 25.2 to 26.5). The female to male incidence rate ratio of CFS/ME was 3.2 (95% CI: 3.0 to 3.4). The incidence rate varied strongly with age for both sexes, with a first peak in the age group 10 to 19 years and a second peak in the age group 30 to 39 years*"[5].
The second study was a systematic review, exploring issues on case definitions for ME/CFS. Thirty eight studies were included, mostly using CDC-1994/Fukuda case definition[6]. The authors concluded that "*classification of patients according to severity and symptom patterns, aiming to predict prognosis or effectiveness of therapy, seems useful. Development of further case definitions of CFS/ME should be given a low priority. Consistency in research can be achieved by applying diagnostic criteria that have been subjected to systematic evaluation*."

WG2 - There are numerous studies on various biomarkers in CFS. Most biomarker analysis was performed in single centres using non standardized assays and various case definitions. Assays based on flow cytometric cell phenotyping or functional assays analysing cytokine production or cytotoxic function are difficult to standardize. Some studies report contradictory data. Moust markers described show alterations in only subsets of CFS/ME patients or wide overlap with controls. There is no diagnostic biomarker available yet.

COST is supported by
the EU Framework Programme
Horizon 2020

WG3 - Very few studies about economic aspects of ME/CFS had been published. Five macroeconomic studies in different populations are found, while seven cost-effectiveness studies had been reported in the peer-reviewed literature. There appeared to have very little involvement of economists in any of these studies. It was suggested to prepare a critical review of these for publication.
WG4 - A survey among the countries has been carried and 9 countries have replied. This survey will be background for identification of Gaps regarding diagnosis and clinical enablers. It was suggested to go through the survey and identify more gaps.
WG5 - Information is collected concerning the first training school planned in year 2 and should be discussed.
WP6 - The EUROMENE website was presented and improvements suggested.
STSM coordinator – The questionnaire had been prepared by Prof. Uldis Berkis in order to find out the pretenders for the 1st year visits and potential host institutions.

3. Other actual questions

As far as STSM coordinator Els Tobback (Belgium) is on maternity leave and vice-coordinator Carmen Adella Sirbu (Rumania) is not present, additional person should be nominated to make STSM activity successful.

Minutes of the 29 September 2016 Work Group meetings:

1. **Discussion on first period work tasks**

Chair **Jesus Castro-Marrero** (Spain), Vice-leader Slobodan Sekulic (Serbia) **WG on epidemiology:** - Explore of ways to collect population based data on the prevalence of ME/CFS, - Explore of the potential of existing cohorts, - Review the characteristics of existing clinical databases maintained by collaborating institutions, - Survey existing epidemiological data on ME/CFS in participating countries.
Chair **Carmen Scheibenbogen** (Germany), Vice-leader Enrica Capelli (Italy) **WG on biomarkers:** - Establish special interest groups within the network able to take fragmented research in a harmonised way, - Survey in EU countries existing data on potential immunological biomarkers of ME/CFS (cytokine profiles, lymphocyte subsets, adjuvant use epidemiology), - Survey in EU countries existing data on potential infection-associated biomarkers of ME/CFS (viral, bacterial and fungal infections), - Survey in EU countries existing data on potential genetic and epigenetic biomarkers, - Survey in EU countries existing data on neuro-imaging biomarkers.

Chair **Derek Pheby** (UK), Vice-leader Julian Blanco (Spain) **WG on socio-economics:** - Survey in EU countries existing data on economic loss due to ME/CFS, - Analyse existing clinical criterions guidelines in order to find-out optimal criteria set allowing excluding over-diagnostic and un-diagnostic, - Develop approaches to calculate direct economic loss due to ME/CFS.
Chair **Elin Bolle Strand** (Norway), Vice-leader Jerome Authier (France) **WG on clinical research enablers and diagnostic criteria:** - Survey clinical criterions used in EU countries to set-up diagnosis of ME/CFS, - Analyse existing clinical criterions guidelines in order to find-out optimal criteria set allowing excluding over-diagnostic and un-diagnostic, - Survey in EU countries existing data on neurological picture of ME/CFS (including association with similar diseases and symptoms, like fibromyalgia), - Analyse the used ME/CFS treatment and its efficacy/safety in order to find-out optimal treatment approaches lowering severity of clinical course.
Chair **Evelina Shikova-Lekova** (Bulgaria) **WG on conferences, seminars, training schools**
Chair **Lorenzo Lorusso (Italy),** Vice-leader Anne Marit Mengshoel (Norway) **WG on dissemination and exploitation, patient involvement, digitalisation:** - Create project webpage, - Survey of existing small/medium-sized enterprises (SMEs) in the pharmaceutical, biotechnology and ICT industries in each participating country in order to develop collaborative research.
STSM coordination - U.Berķis (Latvia) - Develop questionnaire to select candidates for training events.

Minutes of the 30 September 2016 Management Committee meeting:

1. Reports of the WG leaders on the perspective work plans for the next period and realization approaches:

WG1: Work group on epidemiology
WG Leader Jesus Castro-Marrero (Spain)

Participants: Eliana Lacerda (UK), Jean-Dominique De Korwin (France)

The main objectives for WG1 are as follows:
1. To establish an information network for the collection of epidemiological data, in order to estimate the incidence and prevalence of ME/CFS in the EU to better guide research and therapeutic development efforts;

2. To establish a standardised methodology for all member EUROMENE participating countries, for operationalising the chosen diagnostic criteria to the recognition (identification?) of ME/CFS cases;
3. To create a national database for the collection of epidemiological data on ME/CFS at European level, on which to base the foundations of scientific and clinical research;
4. To obtain information on existing – and planned collections of – biosamples, to facilitate clinical research such as the study of potential diagnostic biomarkers for ME/CFS, and further epidemiological studies, such as case-control or cohort studies, with can use biological samples for measuring potential risk factors;
5. To define standardised procedures for the identification of cases and control groups, data collection, and input of data and samples relating to the search;
6. To disseminate scientific findings ME/CFS throughout European countries.

Background

The dissemination of epidemiological information about ME/CFS, including estimates on incidence and prevalence of the disease in Europe will allow the development of new health regulations, with optimised strategies for disease management and improvement of quality of life of those affected. Currently, the scarcity of research funding in the field and consequent lack of reliable and reproducible information, obstruct the ascertainment of available therapies that may improve the patients' conditions.

Additionally, one of EUROMENE's strategies for facing the current paucity of research funding is to optimise resources, by gathering a substantial number of patients and controls participating in research across the EU countries. This strategy would enable us to account for the heterogeneity of ME/CFS, and larger sample sizes that would provide enough power to the studies, and would base future multisite clinical trials, which might be less effective if developed by an individual state.
Furthermore, the collaboration between epidemiologists, molecular biologists, and biostatisticians will allow the development of integrated methods for the evaluation of laboratory-based diagnostic strategies (biomarkers), and further research on molecular epidemiology in the ME/CFS field. Currently there are no specific treatments and diagnostic tests for ME/CFS, but it's very important to raise public awareness of the disease and to provide scientific material to doctors who ignore the existence of a disease that is so heterogeneous and complex.
Finally, the success of EUROMENE Consortium will depend on the involvement of patients, their families, support groups of patients, healthcare personnel, and ultimately the national and local government agencies.

1. Current ME/CFS estimates of incidence and prevalence in Europe

The first step of the WG1 - Epidemiology was to search published estimates of incidence and prevalence of ME/CFS across Europe. We identified two studies that though were not specific for EU countries, considered the main epidemiological studies published studies in European countries.

The first was a meta-analysis aiming to identify variability among estimated prevalence data for ME/CFS according to the case definition and the method of assessment used [1]. Databases were systematically searched for studies on ME/CFS prevalence in adults based on **the 1994 CDC/Fukuda case definition and 2003 Canadian consensus criteria**. Estimates were categorized into two methods of assessment: **self-reporting of symptoms** vs. **clinical assessment of symptoms**. This was also stratified by sample setting (community or primary care). Of 216 records found, 14 studies were considered suitable for inclusion. From these only 3 were based on European population, i.e. the Netherlands [2], Iceland [3], and the UK [4]. However, the latter was removed from the analysis due to its large sample size, according to the meta-analysis' authors, it "*was removed due to its large statistical weighting. If included, the results of the remaining studies would not have been detected by the meta-analysis*" [1]. The pooled prevalence for **self-reporting of symptoms** was 3.28% (95% CI: 2.24–4.33) and 0.76% (95% CI: 0.23–1.29) for **clinical assessment of symptoms**. High variability was observed among self-reported estimates, while clinically assessed estimates showed greater consistency. Contrastingly, Nacul et al found ME/CFS prevalence rates of 0.2% for cases meeting any of the study case definitions, 0.19% for the **CDC/Fukuda**, and 0.11% for the **2003 Canadian consensus criteria** [4].

Few studies estimating incidence of ME/CFS in Europe were published so far. While Nacul at all found "*overall estimated minimal yearly incidence was 0.015%*" For the UK population [4]; Bakken et all, found "*overall incidence rate was 25.8 per 100,000 person years (95% confidence interval (CI): 25.2 to 26.5). The female to male incidence rate ratio of CFS/ME was 3.2 (95% CI: 3.0 to 3.4). The incidence rate varied strongly with age for both sexes, with a first peak in the age group 10 to 19 years and a second peak in the age group 30 to 39 years*"[5].

The second study was a systematic review, exploring issues on case definitions for ME/CFS. Thirty-eight studies were included, mostly using CDC-1994/Fukuda case definition [6]. The authors concluded that "*classification of patients according to severity and symptom patterns, aiming to predict prognosis or effectiveness of therapy, seems useful. Development of further case definitions of CFS/ME should be given a low priority. Consistency in research can be achieved by applying diagnostic criteria that have been subjected to systematic evaluation.*"

The observed heterogeneity in CFS/ME prevalence may be due to differences in method of assessment. Prevalence for ME/CFS based on self-reporting of symptoms alone should be viewed with caution. Clinically valid diagnoses are vital in undertaking accurate prevalence studies for ME/CFS**. The 1994 CDC/Fukuda case definition and 2003 Canadian criteria** appeared to be the most reliable clinical assessment tool available at the time of these studies. Improving clinical case definitions and their adoption internationally will enable better comparisons of findings and inform health systems about the true burden of ME/CFS.

New advances are urgently needed for standardised application of clinical case definitions, for example, for using the 2003 Canadian criteria and recently proposed 2015 NIH/IOM definition for SEID diagnostic criteria. Consequently, further estimates of incidence and prevalence studies may be expected.

2. Current information on the existing ME/CFS biobank and sample collections, and protocol for a brain tissue bank

Our aim, having previously investigated through a qualitative study involving extensive discussions with experts and ME/CFS patients the issues involved in establishing and maintaining a disease specific brain, tissue and biosamples bank for ME/CFS, was to develop a

protocol for a UK ME/CFS repository of high quality human sampling from well diagnosing subjects with ME/CFS and matched controls suitable for a broad range of research applications. This would involve a specific donor program coupled with rapid collection and processing of tissue and blood biosamples, supplemented by comprehensive prospectively collected clinical, laboratory and self-assessment data from cases and matched controls. On this basis, we developed the protocol presented here, which was designed to meet high technical and ethical standards and legal requirements and was based on recommendations of the MRC UK Brain Banks Network. The facility would be most efficient and cost-effective if incorporated into an existing tissue bank. Both tissue and biosamples collection would be rapid and follow robust protocols to ensure preservation sufficient for a wide range of research uses. A central bank would have resources both for wide-scale donor recruitment and rapid response to donor death for prompt harvesting and processing of tissue and biosampling. ME/CFS brain, tissue and blood samples bank could be established using this protocol. Success would depend on careful consideration of logistic, technical, legal and ethical issues, continuous consultation with patients and the donor population, and a sustainable model of funding ideally involving research councils, health services, and patient charities. This initiative could revolutionise the understanding of this still poorly-understood disease and enhance development of diagnostic biomarkers and treatments. Besides, there are biological sample collections in Norway (ME/CFS Biobank in Oslo University Hospital), in Spain (Vall d'Hebron Univ Hospital, Barcelona), in Germany (Berlin Charité Hospital), and also in Italy (Pavia -Enrica and Lorenzo).

We have established the need for the structured collection and examination of nervous system human tissue and biofluids of ME/CFS case who have died. Based on the experience at Addenbrooke's Hospital and other brain banks, and building on information given by experts and by patients themselves, we have developed a protocol for the first ME/CFS Tissue Bank in the world, including carefully chosen approaches for recruiting and following-up donors and for collecting, storing and examining post-mortem tissue and blood samples. This initiative has the potential to revolutionise the understanding of this still poorly recognised disease and greatly help the development of more precise case definitions, diagnostic biomarkers, and personalized treatments.

3. Guidelines on ME/CFS biobank management and maintenance

The current protocols for biobank and post-mortem tissue bank can be used as reference for the process of harmonising and standardising the protocols across the participating countries in Europe.

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3. Lindal E, Stefansson JG, Bergmann S. The prevalence of chronic fatigue syndrome in Iceland - a national comparison by gender drawing on four different criteria. Nordic journal of psychiatry. 2002;56(4):273-7

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6. Brurberg KG, Fonhus MS, Larun L, Flottorp S, Malterud K. Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review. BMJ open. 2014;4(2):e003973

WG2: Work group on biomarkers

WG Leader Carmen Scheibenbogen (Germany)

Participants: Enrica Capelli (Italy), Evelina Shikova-Lekova (Bulgaria), Julia Blanco (Spain), Thomas Harrer (Germany), Henrik Nielsen (Denmark), Zaiga Nora-Krukle (Latvia), Santa Rasa (Latvia), Jerome Authier (France), Carmen Scheibenbogen (Germany).

People who expressed their interest to join, but couldn`t participate: Jonas Bergquist (Sweden), Madlen Löbel (Germany), Svetlana Orlova (Belarus), Eleanor Riley (UK), Jackie Cliff (UK), Bhupesh Prusty (Germany), Giovanni Ricevuti (Italy), Prof. Scire (Italy).

Background

There are numerous studies on various biomarkers in CFS. Most biomarker analysis was performed in single centres using non standardized assays and various case definitions. Assays based on flow cytometric cell phenotyping or functional assays analysing cytokine production or cytotoxic function are difficult to standardize. Some studies report contradictory data. Most markers described show alterations in only subsets of CFS/ME patients or wide overlap with controls. There is no diagnostic biomarker available yet.

Selected reviews published recently:

1. Jason LA, Zinn ML, Zinn MA. Myalgic Encephalomyelitis: Symptoms and Biomarkers. Curr Neuropharmacol. 2015: 701-34. Review.
2. Blundell S, Ray KK, Buckland M, White PD. Chronic fatigue syndrome and circulating cytokines: A systematic review. Brain Behav Immun. 2015 Nov; 50: 186-95.
3. Fischer DB, William AH, Strauss AC, Unger ER, Jason L, Marshall GD Jr, Dimitrakoff JD. Chronic Fatigue Syndrome: The Current Status and Future Potentials of Emerging Biomarkers. Fatigue. 2014 Jun 1; 2: 93-109.
4. Klimas NG, Broderick G, Fletcher MA. Biomarkers for chronic fatigue. Brain Behav Immun. 2012 Nov; 26: 1202-10.

Summary of the WG2 meeting outcome: Due to the complexity of the biomarker studies in CFS it was decided to focus activities on topics of interest, which will be chaired by the indicated

persons: Immunology (Carmen Scheibenbogen, Julia Blanco), Genetics (Enrica Capelli), Chronic vial infections (Thomas Harrer, Santa Rasa, Zaiga Nora-Krukle, Evelina Shikova-Lekova, Neurology (Jerome Authier) and metabolis (Jonas Bergquist to be asked).

It was agreed to work on the following 2 aims as defined by the MoU until the next meeting:

1. Survey on biomarker to establish an „**European biomarker landscape**";
2. Establish special interest groups within the network able to take **fragmented research** in a harmonized way.

To achieve the 1st aim a questionnaire will be sent to MC members of each country to identify the national research groups. We will ask to perform a Pub Med Screening, too, to identify active biomarker research group. For the search the key words „Chronic fatigue syndrome" and „country" should be used and a filter for the last 5 years chosen. By this search, e.g., for Germany 62 hits, Spain 59 hits, Great Britian 46 hits are retrieved. Chronic fatigue syndrome is a MeSH term including ME, and various other definitions.

The 2nd aim is more difficult to achieve as there is no money for research available within the EUROMENE network yet. A first application for research funding was prepared by Luis Nacul and Eliana Lacerda and finalized during the meeting. As a first step it was decided to evaluate the published literature and to identify biomarkers of interest, which might be retested within labs of our group.

Based on the literature research and our own experience we plan to write so called critically appraisal topic reviews, which we want to publish as an effort of the EUROMENE network.

It was agreed to work on the following topics:

- Persistent infection markers (Thomas Harrer, Santa Rasa, Zaiga Nora-Krukle);
- Genetic markers (Enrica Capelli);
- Immune phenotype markers (Julia Blanco);
- Complement markers (Henrik Nielsen);
- Autoimmune markers (Carmen Scheibenbogen, Madlen Löbel).

The next WG meeting will be on 27.1.17 in Berlin. Until then data for the European landsacape should be surveyed (Madlen Löbel, Carmen Scheibenbogen) and summarys from our reviews prepared and presented and preferably a first draft written (people listed above and everybody else who is interested to work on these selected topics).

WG3: Work Group on socio-economics

WG Leader Derek Pheby (UK)
Participants: Derek Pheby (UK), Uldis Berkis (Latvia), Asja Lunga (Latvia).

1. Literature review. The literature review undertaken by Derek Pheby (DP) had identified that very few studies about economic aspects of ME/CFS had been published. He had found five macroeconomic studies in different populations, while seven cost-effectiveness studies had been reported in the peer-reviewed literature. There appeared to have very little involvement of

economists in any of these studies. DP suggested that it could be useful to prepare a critical review of these for publication.

2. Recruitment of health economists. DP reported that he had had responses to his appeal in the Health Economics Study Group's newsletter from eight very well qualified health economists (4 from the UK, 1 each from Ireland and the Netherlands, and 2 from Italy). This was very much in line with the COST philosophy of fostering academic research networks across national boundaries, and had created a resource not before available in ME/CFS research. There was discussion about how best to integrate these volunteers into the COST action.
Uldis Berkis (UB) suggested that they could be involved in year 2 as trainers in one or other training event to be held next year, and some could perhaps attend the Barcelona meeting arranged for year 2. He further suggested that a possible means of funding their involvement could be through the ELSA (Ethical, Legal, Social) program, which is part of Eva-Net Neuron. There is also a one-day meeting for Working Groups arranged for 27th January in Berlin, to which they could be invited. He pointed out that, where such volunteers came from countries not already part of the action, their involvement could effectively mean that those countries could be signed up to participate in COST, which, if it happened in year 1, would have a positive impact upon the project budget in year 2. This could make the involvement of such volunteers easier to fund. DP will respond to the volunteers, and UB will look further into these possibilities.

3. Current status of economics data in participating countries. For most European countries, there was very little if any data on the costs and losses attributable to ME/CFS, and in any case the multiplicity of health care and data recording systems meant that there was really no basis for transnational comparisons. The questionnaire on data quality and comparability circulated to EUROMENE participants and interested parties (some 100 in total) by DP as part of his attachment to RSU in the BALTINFECT project should create a better platform for determining data compatibility, and facilitate such comparisons. DP will shortly reminder to non-respondents, prior to analyzing responses.
UB will look into the possibility of linking ECDC data from Latvia (including cost data) with equivalent data from other countries.

WG4: Work group on clinical research enablers and diagnostic criteria

WG Leader Elin Bole Strand

A survey among the countries has been carried and 9 countries have replied. This survey will be background for identification of Gaps regarding diagnosis and clinical enablers.

There were five persons in the work group (Italy, UK, Latvia, France and Norway). The survey was discussed and focus was on questions regarding diagnosis.

The following gaps were identified at this point:

1. National guidelines: four countries do not have national guidelines. For those having guidelines different guidelines are recommended and applied. Also some countries have and use criteria for children while others do not.

2. Test for diagnosis/symptom registrations: different questionnaires and tools may be applied in different countries to assess CFS/ME symptoms.
3. Exclusion/differential diagnosis: guidelines and standard tests for the exclusion part are unclear/ various. Some of the countries have multidisciplinary team working with this patient group and some do not. Some do additional psychological/psychosocial, neurological/ neuropsychological as well as other examinations. Some do either one or another examination often depending on what kind of specialists they have in the team, at the institution or that are available. Standardized questionnaires are applied in the exclusion part in some of the countries, but also what kind of tests/questionnaires varies between them. There is a lack of more specific guidelines for indication for further examinations of the patients.
4. Severe ill patients may not be diagnosed in some countries as the prevalence seems to vary from hardly existing to 5 or 25% of the ME/CFS population
5. Education of health providers for diagnosis of ME/CFS varies greatly between the countries.
It will be continue to go through the survey and identify more gaps.
A summary and report from the rest of the survey will be written by the group leaders and discussed further in the work group.
It was also discussed to meet to work together (apply for STSM), and to invite experts (Professor Jason at DePaul University) for future WG meetings.

WG5: Work Group on conferences, seminars, training schools

WG Leader Evelina Shikova-Lekova (Bulgaria)

1. **Information on forthcoming meetings by the end of the first period:**
   - Berlin 27 January, 2017: one-day Working group meeting about synchronization progress agenda of the meeting is under preparation and will be distributed soon;
   - Barcelona 16-17 March, 2017: Second Core groups meeting, Work group meeting, First Workshop;
2. **Information and discussions concerning the first training school planned in year 2:**
   - Topic - Molecular biomarkers for ME/CFS;
   - Place/Local organizers - Pavia (Italy), UNIVERSITA DEGLI STUDI DI PAVIA/ Enrica Capelli and Lorenzo Lorusso;
   - Will be combined with MC and CG meetings;
   - All other issues concerning timing, training program, trainees, trainers, etc will be further discussed.

WG6: Work Group on dissemination and exploitation, patient involvement, digitalisation

WG Leader: Lorenzo Lorusso (Italy)

Participants: Italy, Latvia.

1. A presentation of the Euromene website and suggested improvements about some aspects:

- a reduction of the text;
- specify the involvement of each members of the cost action Euromene;
- emphasize the role of each WG in the Project.

2. The future activities:

- update of deliverables in the site of the each WG in Riga,
- an involvement of the association of patients with a list of them in the website and a possible meeting.

3. Approval of short - term visits' plan:

At present there are 3 early carrier researchers' applications for Latvia wishing to be trained in cell subpopulation detection, biochemical markers and clinical features of ME/CFS.

4. Report of Dr. Eliana Lacerda and Dr. Luis Nacul on the project draft for the Horizon 2020 (application is finished and send in at present);

5. Dr Eliana Lacerda presentation for the Fort Lauderdale, USA meeting (could be fined in Internet and COST website);

6. Discussion and other actual questions:

Dr Magdalena Budisteanu is nominated and has agreed to work as STSM coordinator during the Els Tobback (Belgium) maternity leave.

7. Concluding remarks - Modra Murovska, Eliana Lacerda, Uldis Berķis