

COST action CA15111

European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

**Minutes of the Management Committee meeting and
Work Group No 2, No 4 and No 5 meetings,
20 - 21 November 2019, Berlin, Germany**

CA15111 MC Chair: Modra Murovska

Local Meeting Chair: Carmen Scheibenbogen

Welcome: Carmen Scheibenbogen, Modra Murovska

Management Committee meeting

Participants: Modra Murovska, Eliana Lacerda, Jonas Bergquist, Fernando Estévez López, Slobodan Seculic, Jesus Castro-Marrero, Carmen Scheibenbogen, Thomas Harrer, Ingrid Helland, Jean-Dominique Korwin, Jérôme Authier, Luis Nacul, Evelina Shikova-Lekova, Lorenzo Lorusso, Anne Marit Mengshoel, Hendrik Nielsen, Olli Polo, Nuno Sepúlveda, Ruud Vermeulen, Francisko Westermeier, Pawel Zalewski, Svetlana Orlova.

Modra Murovska (*Prezentācija_MM_Berlin_November_2019*)

1. Content of the presentation

- Progress – what is done:
 - i. STSMs;
 - ii. ITC Conference grants;
 - iii. Publications planned/submitted or manuscripts prepared.
- What should be done:
 - i. Deliverables;
 - ii. Skype conference with partner organizations;
 - iii. About e-voting etc.

2. STSM grants are used according to the GP4 plan:

- A. Natasa Hinic (Serbija). Practical approach in a herpes-, papilloma- and polyoma diagnostic as infection-associated biomarkers of ME/CFS. 12-19 August, 2019. STSM to National Center of Infectious and Parasitic Diseases, Bulgaria (Prof Evelina Shikova-Lekova). **1580 EUR**
- B. Stefania Diaconu (Romania). Sleep medicine. 9-21 September, 2019. STSM to Paris East-Creteil University, Paris, France (Prof François Jérôme Authier). **2380 EUR**
- C. Francisco Westermeier (Austria). Application of multivariate statistical methods to identify subgroups of ME/CFS patients. 18 August - 1 September, 2019. STSM to London School of Hygiene and Tropical Medicine (LSHTM), UK (Dr Nuno Sepúlveda). **2500 EUR**

- D. Maria Rodriguez Garcia (Spain). Brain structure and function in children with chronic fatigue syndrome. 01-14 October, 2019. STSM to Department of Child and Adolescent Psychiatry, Gent University, Netherlands (Dr Fernando Estévez López). **2500 EUR**
- E. Diana Araja (Latvia). Investigation of opportunities to use the patient reported outcomes in evaluation of socio-economic impact of ME/CFS on society. 03-13 December, 2019. STSM to University of Pavia, Italy (Prof Cinzia Di Novi). **1050 EUR**
- F. Sabine Gravelšina (Latvia). Molecular methods to study ME/CFS biomarkers. 08-22 February, 2020. STSM to the Catholic University of Valencia "San Vicente Mártir", Spain (Prof Elisa Oltra). **2250 EUR**.

3. Presentations – ITC Conference Grants (7175/12500 EUR)

- A. Tiago Domingues (Portugal). Analysis of serological data towards a better understanding of the aetiology of ME/CFS. 40th Annual Conference of the International Society for Clinical Biostatistics. 14-16 July, 2019, Leuven, Belgium. (Poster presentation). **1090 EUR**
- B. Diana Araja (Latvia). Medication preferences of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients. 79th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2019, 22-26 September, 2019, Abu Dhabi, United Arab Emirates (Poster presentation). **2220 EUR**
- C. Anda Vilmane (Latvia). Presence of parvovirus infection markers among patients with encephalopathy. 22nd European Society for Clinical Virology's Annual Meeting, ESCV 2019, 11-14 September, 2019, Copenhagen, Denmark. (Poster presentation). **1400 EUR**
- D. Diana Araja (Latvia). Economic burden of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) to patients: comparative study. ISPOR Europe 2019 (International Society for Pharmacoeconomics and Outcomes Research), 2-6 November, 2019, Copenhagen, Denmark (Poster presentation). **1175 EUR**
- E. Joanna Słomko (Poland). Differences in mineral levels may be related to symptoms of chronic fatigue syndrome. 25th International Conference on Clinical Nutrition, March 02-03, 2020, Rome, Italy. (Poster presentation). **1290 EUR**

Balance: 5325 EUR

4. Planned publications

- A. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Investigating care practices pointed out to disparities in diagnosis and treatment across European Union (20/11/2019), *PLoS One* (Submitted);
- B. Scoping review about: Effects of non-pharmacological intervention and ME/CFS patients' experiences of participation in such interventions (31/12/2019), *PLoS One or Medicia MDPI*;
Effects and patients' experiences of non-pharmacological treatment for myalgic encephalomyelitis/chronic fatigue syndrome – a scoping review from the EU-Cost group EUROMENE network. Submitted to *Health Expectations* on 12/11/2019 (Prof Anne Maritt Mengshoel);
- C. Summary of evaluated socio-economic direct and indirect costs caused by ME/CFS in Europe (25/06/2019), *Frontiers*
The Development of a Consistent, Europe-Wide Approach to the Investigation of the Economic Impact of Myalgic Encephalomyelitis (ME/CFS); a report from the European Network EUROMENE, manuscript prepared for submission to *Frontiers* (Prof Derek Pheby);

- D. Cytomegalovirus, Epstein-Barr virus and Human Herpesvirus 6 Infections in Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Submitted to *Journal of Neurovirology* (Prof Evelina Shikova-Lekova). Co-authors from Bulgaria, Serbia, Latvia;
- E. Cognitive impairment in ME/CFS (25/06/2019), *Frontiers or PLoS One* or another open access journal;
- F. Review on functional studies and routine laboratory assays which may aid in the diagnosis and differential diagnosis of ME/CFS (20/01/2020), *Translational Medicine or PLoS One* or another open access journal.

5. Deliverables not delivered

Deliverable 11 (30 month) - Evaluation scales for assessment of neurological symptoms associated with ME/CFS and usable in diagnostic – 30 November 2018 WG2 → WG4

Deliverable 12 (31 month) - Common strategy protocol for ME/CFS diagnosis: synchronisation between centres, research component integration - 31 December 2018 → WG4

Deliverable 13 (36 month) - Protocol and guidelines for ME/CFS subgroups detection (stratification) according to the presence of symptoms and subject to potential biomarkers variation - 30 April 2019 → WG4

6. Deliverables

Deliverable 14 (38 month - 05.2019; Submitted 14.11.2019) - Collaborative research project on ME/CFS based on synergy with other initiatives and resources integration 31 May 2019 → WG6.

H2020-WIDESPREAD-05-2020-Twinning, submitted project “Reducing networking gaps between Rīga Stradiņš University (RSU) and internationally leading counterparts in viral infection-induced autoimmunity research (Latvia, Germany, Italy, Israel), VirA.

Deliverable 15 (45 month - 12.2019) - Synchronized proposal for guidelines for management/treatment of ME/CFS: accommodating the existing and emerging therapies 31 December 2019 → WG4

Deliverable 16 (47 month - 02.2020) - Program book/abstract book and overview of final global conference and conclusions 28 February 2020 → WG6

Deliverable 17 (48 month - 03.2020) - Guidelines for health policy makers on prevention losses due to ME/CFS in health and economy aspects in Europe 31 March 2020 → WG3

7. Skype Conference with patient organizations

- i. Date of conference identified (responsible person);
- ii. Patients organizations identified and invited (partially done by Lorenzo Lorusso);
- iii. Program of conference drafted (responsible person, date);
- iv. Outcome of the conference.

8. Conference

Final global conference “Common strategy on research of ME/CFS” and MC meeting

Dates: 12/03/2020 – 13/03/2020

Location: Riga (Latvia)

Participants: 50

Travel costs: 18270 EUR

Local organizer support grant: 0

Outputs: Conference program; program book/abstract book and overview of final global conference. The collaboration resulting from this Action will strengthen the already existing collaborations of several partners and lead to new interdisciplinary exchanges on topics which currently are disadvantaged by absent or low level communication. This Action will provide the opportunity to expand collaborations by the provision of meetings and trainings. As a result, the establishment of new contacts is expected with teams working in other disciplines or using different methodologies. MC members voted to cut daily allowance from €120 to €80 to secure a higher number of members at the conference.

9. CA15111 // COST INNOVATORS' GRANT: invitation to apply

Successful applications will get a financial support of maximum EUR125.000 for the period 1st May 2020 - 30th April 2021. Up to 5 CIGs are expected to be approved, subject to budget availability.

The deadline for the APPLICATION is 31ST JANUARY 2020, AT 12:00 (CET)

As announced, a webinar will take place on the 21st November 2019 at 11.00 (Brussels time) to present in detail the CIG scheme and give you the opportunity to ask any questions. Should you be interested in attending the webinar, please register through this link: https://zoom.us/webinar/register/WN_mkrtzpECSCyLByy7aWYSyw.

After registering, you will receive a confirmation email containing information about joining the webinar. Should you have any questions or encounter any technical issue with the registration, please contact us at cig@cost.eu.

10. About a course of action for requesting EU funding for ME/CFS. Dr Eliana Lacerda

About drafting of a Case for Funding based on the findings from the WGs, and request the EUROMENE e-vote to be able to present it to Mr. Berkouk, on behalf of the 21 EU participating countries.

Work Group No 2 - on Biomarkers meeting

Participants: Modra Murovska, Angelika Krumina, Eliana Lacerda, Luis Nacul, Nuno Sepulveda, Slobodan Sekulic, Ruud Vermeulen, Joanna Slomko, Jerome Authier, Francisko Westermeier, Jesus Castro, Henrik Nielsen, Olli Polo, Fernando Estevez, Ingrid Helland, Pavel Zalewski, Anne Mengshoel, Henrik Nielsen, Jonas Bergquist, Svetlana Orlova, Evelina Shikova-Lekova, Uta Behrends, Thomas Harrer, Bhupesh Prusty, Franziska Sotzny, Helma Freitag, Sebastian Lorenz

WG 2+4 joint session

ME/CFS subgroup detection/stratification according to symptoms and biomarkers

- 1. ME/CFS subgroups - What is known?**
- 2. Multiparameter studies on clinical data and lab values**
 - London cohort, Eliana Lacerda
 - Berlin cohort, Sebastian Lorenz
 - Other cohorts to be discussed
- 3. Functional studies**
 - Physical fatigue/muscle power London + Berlin cohort

- Autonomic assessment, Pawel Zalewski
- Endothelial function in ME/CFS, Franco Westermeier
- Other tests tbd

WG2 Biomarker studies

- Strategy paper for biomarker development
- Presence of autoantibodies against adrenergic and muscarinic receptors in two Swedish ME/CFS cohorts, Jonas Bergquist
- EBV antibodies in ME/CFS, Nuno Sepulveda

In the joint session with WG4 the topic was subgroups in ME/CFS. First clinical evidence for existence of subgroups was discussed. Eliana Lacerda then presented data from the London cohort on differences in lab parameters in patients with moderate vs severe ME/CFS. Sebastian Lorenz showed data from the Berlin cohort on subgrouping of patients according to autonomous nervous system symptoms. Helma Freitag from Berlin presented a study on repeat assessing of handgrip power to assess muscular fatigue. Pawel Zalewski from Poland gave an overview on testing of autonomous nervous system dysfunction and results in ME/CFS and Franco Westermeier from Austria on endothelial dysfunction. This was followed by discussion and the decision to write a consensus paper.

Then WG2 and 4 separated and WG2 reviewed and discussed recent biomarker studies. Nuno Sepulveda presented a study on the diagnostic utility of IgG responses against EBV peptides and Jonas Bergquist presented a Swedish cohort study on antibodies against adrenergic and muscarine acetylcholine receptors in serum and spinal fluid of ME/CFS patients and controls. It was decided to write a joint paper including clinical, functional and biomarker data to define subgroups of ME/CFS paper including a recommendation on bioinformatic analysis of such data.

Work Group No 4 on Clinical research enablers and diagnostic criteria meeting

Participants: Jerome Authier, Luis Nacul, Modra Murovska, Angelika Krumina, Eliana Lacerda, Nuno Sepulveda, Slobodan Sekulic, Ruud Vermeulen, Joanna Slomko, , Francisko Westermeier, Jesus Castro, Henrik Nielsen, Olli Polo, Fernando Estevez, Ingrid Helland, Pavel Zalewski, Anne Mengshoel, Henrik Nielsen, Jonas Bergquist, Svetlana Orlova, Evelina Shikova-Lekova, Uta Behrends, Thomas Harrer, Bhupesh Prusty, Franziska Sotzny, Helma Freitag, Sebastian Lorenz

WG 2+4 joint session

ME/CFS subgroup detection/stratification according to symptoms and biomarkers

Multiparameter studies on clinical data and lab values

1. Olli Polo. Communication on Low-Dose Naltrexone (LDN) in the Treatment of ME/CFS. This work is a retrospective study analyzing the effects of LDN 3.0 -4.5 mg/day (1.5mgx2/d; dose increased at 4.5mg/j after 6 wks) in 218 patients with ME/CFS: positive response in 74%, no response in 14%, mild/temporary adverse effects (insomnia, nausea, dizziness, headache or nightmares) in 54%, responsible of treatment discontinuation in 7.3% (no serious adverse effect reported). The paper is published in *Fatigue: Biomedicine, Health & Behavior* (<https://doi.org/10.1080/21641846.2019.1692770>).

Cohort studies

2. Eliana Lacerda/Luis Nacul (UK) presented data from London cohort. Diagnostic criteria are CDC-1994, CCC-2011, SEID-2015. Controls are healthy individuals (HC), and MS patients (patients with MS, PWMS). Chronically fatigued patients are stratified in 3 groups: (i) ME/CFS, mild/moderate; (ii) ME/CFS, severe; (iii) non-ME/CFS chronic fatigue. Database includes a total number of 514 registered persons with clinical assessment and blood samples (baseline, follow-up). Clinimetric evaluation with SF-36v2 showed a worsening or improvement with time, in a small proportion of patients. The exploitation of this database produced a number of studies dealing with: (i) functional states and well-being; (ii) CK levels changes in ME/CFS patients (significant CK decrease in patients with severe ME/CFS); (iii) cellular immune functions (evidence for increased effector memory CD8⁺ T-cells, decreased terminally differentiated effector CD8⁺ T cells, significantly increased mucosal associated invariant T cells in ME/CFS patients; unchanged NK cell numbers in contrary to previous reports); and (iv) hand grip strength as a biomarker for ME/CFS and disease severity.

3. Sebastian Lorenz (Germany) presented data from Berlin cohort. The database includes 571 patients with clinically confirmed ME/CFS (CCC criteria), with infectious or non-infectious type of onset. Clinimetric parameters include Bell CFIDS disability scale, Chalder fatigue scale, SF-36, COMPASS score for dysautonomia. The presentation pointed out the correlations between autonomic dysfunction and other key features of ME/CFS, such as cognitive impairment.

Functional studies

4. Pawel Zalewski (Poland) presented a report on the usefulness of autonomic assessment in ME/CFS. COMPASS 31 disclosed a high proportion of ME/CFS patients with symptoms consistent with orthostatic intolerance. PoTS is found in 51% of patients. Autonomic symptoms were found correlated with lower quality of life. Specific evaluations (heart rate and non-invasive continuous blood pressure measurements at rest and on standing) disclosed impaired blood pressure variability. Preliminary results with MIBG imaging (quantitative measure of cardiac sympathetic innervation) indicate that impaired cardiac MIBG uptake was associated with increased fatigue severity in CFS.

5. Assessment of physical fatigue/muscle power (London + Berlin). Handgrip strength (HGS) was evaluated by London group as a diagnostic marker in ME/CFS. They showed that HGS is

markedly reduced in ME/CFS, particularly in patients with more severe disease, and may indicate muscle and fatigue related symptoms (results published in *Front Neurol.* 2018; 9:992).

General discussion

- Paper entitled "Myalgic Encephalomyelitis/Chronic fatigue Syndrome (ME/CFS): Investigating care practices pointed out to disparities in diagnosis and treatment across European Union" has been published in PLoS One on behalf of EUROMENE and is accessible with weblink:
(<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0225995>)
- The draft of review paper dealing with cognitive impairment in ME/CFS will be sent to WG4 members and neurologists in Euromene, then to all Euromene members.
- Text dealing with Euromene recommendations for the diagnosis, the investigations (specialized clinical testing such as neuropsychological evaluation, lab tests including biology, electrophysiology, neuroimaging), treatment and care organization will be produced, with writing an article to be published in an international journal.

WORK GROUP No 5 - Work Group on conferences, seminars, training schools meeting

WG Leader Evelina Shikova-Lekova (Bulgaria)

1. Information on the meetings during the GAP4 of COST action CA15111
2. Information and discussions concerning EUROMENE Final Conference - main decisions:
 - Title: Common strategy on research of ME/CFS;
 - Location: Riga, Latvia;
 - Dates: 12th to 13th March 2020;
 - Local organizers: Rīga Stradiņš University. Members of local organizing committee will be proposed and specified by Latvian partner ASAP, including e-mail for contact;
 - Scientific committee – EUROMENE Chair, Vice Chair, WG leaders;
 - Will have 4 sessions corresponding to the WG1-4 topics - ME/CFS epidemiology, ME/CFS biomarkers, ME/CFS socio-economics, ME/CFS clinical research. Will be combined with final MC meeting – after scientific sessions;
 - Planned 50 participants, of them 21 reimbursed from COST. The Grand Holder will ASAP identify possibility for ITC Conference Grants and funding of travel expenses of invited speakers;
 - All other participants (not members of the MC of COST Action CA15111 and not invited by e-COST) in the Final meeting will have to cover their travel expenses by themselves. Decision concerning “registration fee” will be taken later (ASAP);
 - Each session includes keynote presentations (one of them by WG leader) and at least 3 short presentations. Most presentations are by COST Action CA15111 participants, including MC substitutes. In case there will be possibility for inviting other people, we will increase later the number of presentations, including poster presentations;
 - WG1-4 Leaders are responsible for selecting scientists for key-note and short presentations. By 5th of December they have to send information about presentations (key-note presentations and 3 short presentations) to WG5 leader;
 - Poster presentations are also possible;

- Publication of abstracts – electronic;
- Information concerning Final Conference – on EUROMENE and Rīga Stradiņš University websites.