Activity Report June-September 2018

This Activity Report gives an overview of the work that has been done in the Work Packages and Subnetworks from June-September 2018.

WORK PACKAGES

Work Package 1 Coordination & Management - Maurizio Scarpa, Cinzia Bellettato, Corine van Lingen

The Coordination Office (CO) has finished writing and submitting the application for the 3-5 year Grant for Chafea/European Commission. The template that is provided by Chafea is very strict and limits us to 30 pages. We will attach the application when we sent to this Activity Report. We have also organized Teleconferences with all the Work Packages and Subnetworks. The next rounds of TC's will take place in November; dates will be send out soon. From then on, the Single Points of Contacts from the patient side will also be invited to these meetings.

Work Package 2 Dissemination - Mireia del Toro

This Work Package has send out the monthly newsletters, kept the website up to date, managed the Facebook, LinkedIn and Twitter accounts. We would appreciate if all HCPs become followers of these accounts in order to increase our social media footprint. WP-2 has also developed two abstracts on MetabERN for the SSIEM meeting.

Work Package 3 Evaluation -Viktor Kozich

The WP on Evaluation has finalized the Survey on HCPs needs and expectations and sent it out to all the HCPs that are members of MetabERN. This WP has worked with WP-1 on the development of the monitoring requirements that we will be communicating on further soon.

Work Package 4 Guidelines/Care Pathways and Standardisation for Medical Care and Transition- Ursula Plöckinger, Carlo Dionis Vici, Maria Luz Couce

The electronic platform (Google Drive) is available and working and accessible for all those who have the link (which has been sent out earlier this year (but can be find here as well). If using the platform, make sure to read the manuals and step-by-step Guide and consult the person responsible for Guidelines in your SNW). The standardized forms of CPRs will be available soon. Specific emphasis was directed to guarantee utmost transparency on the process of setting up CPRs, with respect to the literature used, the persons involved and the quality

criteria (according to AGREE II and Grade). Detailed "how to do" as well as necessary forms are available as matrices facilitating the use of the platform. Two groups are already active in using the platform for their first CPR.
Due to her busy clinic schedule, as well as the writing of her thesis, Athanasia Ziagaki has withdrawn from this WP. Ursula Plöckinger has retired but has offered to take over the guidance of the SNWs for the drafting of GL.

Work Package 5 Virtual Counseling Terry Derks, Klaus Mohnike

The hospital in Magdenburg that dr. Klaus Mohnike is working is starting to work in integrating their hospital system with CPMS. This integration will facilitate data input into CPMS since the data entered into the hospital system will be automatically transferred into CPMS. Terry Derks and Phd student Dr. Alessandro Rossi have developed an education platform for students.

Work Package 6 Research, Translational Activities and Clinical Trials-Maurizio Scarpa, Cinzia Bellettato, Jean-Michel Heard

This WP has been working on the MetabERN Questionnaire on Access to Specialized Treatment and Orphan Medicinal Products for Rare Metabolic Disorders. This questionnaire is intended to provide information about the access, prescription and use of 28 drugs approved by the European Medicines Agency for the treatment of rare diseases. Data will be analysed to identify the challenges and disparities with regard to access to EMA approved medicines within EU Member States.

Work Package 7 Capacity-building and Education-Nadia Belmatoug

The following persons are represented from the SNWs in this WP.

Subnetwork	**Representative**
AOA	Dries Dobbelaere
C-FAO	Philippe Labrune
LSD	Dominique Roland
PD	François Eyskens
PM-MD	Manuel Schiff
CDG	Pascale De Lonlay
NOMS	Angela Garcia Cazorla
Single Point of Contact (SPOC) Patients	Anne Hugon

This WP has been focusing among others on setting up the collaboration between the SSIEM academy and MetabERN. In Athens discussions have been taking place on the first programme on the transition from childhood to adulthood in inherited metabolic diseases. Furthermore, this WP has been planning to set up an interesting clinical case on the MetabERN Education website. Please have a look at this site (via the MetabERN website) to see what news there is.

Work Package 8 Continuity of Care- Trine Tangeraas, Yngve Thomas Bliksrud

WP-8 has made progress in establishing cooperation between MetabERN, ERNDIM and Orphanet. The plan is to use and update the existing ERNDIM database/system in Basel with possible economical support from MetabERN. The plan is to connect the biomarkers in the ERNDIM system with Orphanet-database (disease oriented). With regard to the access to genome-wide genetic investigations for undiagnosed patients with complex disorders, WP-8 is planning

a survey to MetabERN-members to explore the access to genome-wide genetic investigations. WP-8 is also planning to send out an Excel-sheet to all 69 HCPs in order to gather information on available diagnostics in –house, accredited or external in laboratories used by HCPs.

Subnetworks

Amino and organic acids-related disorders (AOA)- Henk Blom, Stefan Kölker, Francjan van Spronsen

- **WP-4 Guidelines**
  - Recommendations for isovaleric aciduria

  Systemic literature search and evaluation, identification of topics of the guideline, formulation of recommendations, formal consensus. Draft version to be circulated for external review, finalization and publication Dobbelaere, Ensenauer

  To be presented and discussed during E-IMD Members Meeting (13th November 2018, Brussels)
  - Recommendations for methylmalonic and propionic aciduria E-IMD consortium has already published evidence-based recommendations for MMA and PA patients. Translate these recommendations into clinical pathway recommendations according to MetabERN
  - Organ transplantation for individuals with organic acidurias and urea cycle disorders

  Project partners have met during the SSIEM conference in Athens (4th September) to identify a strategy for describing and evaluating current practice of organ transplantation in these disease groups in Europe.

  A tentative list of research questions and variables has been established prior to the meeting.

  A survey will be prepared and circulated among AOA members, a draft version of the study analysis plan will be revised and finalized.

  Williams, Molema, Dionisi Vici, Hörster, de Lonlay, Tangeraas

  Collaboration with ERKNet and CERTAIN/CERTAINLI

- **Patient registry (U-IMD)**

Management: Kick-off meetings (Luxembourg and Frankfurt), Workshop meeting (Heidelberg), monthly TCs

- Dissemination: Launching a webpage (https://u-imd.org/), circulation of a leaflet (SSIEM and via webpage) to inform about the activity, presentation of results
- Registry: Establishing a data model Programming of the registry, launching the registry (01/2018), entering patient data (U-IMD in collaboration with MetabERN), evaluation (multiple stakeholders, including PO groups)

Peroxisomal Disorders (PD)- Marc Engelen, François Eyskens

- **WP-2 Dissemination:** Francois Eyskens has been co-author of a paper in the Frontiers in Neurology on White matter lesions in a 16-year old in Fabry. A link can be found here. The SNW has attended the MetabERN meeting at SSIEM and the WP7 meeting on Transition in Athens (3 September, 2018). The SNW has also organized an internal meeting to focus on the activities of PD in the future.

- **WP-4 Guidelines:**
  - A guideline and flyer of Transition of patients with IMD from pediatrics to Internal Medicine at UZA has been set up. A separate guideline will be set up for patients affected by neurometabolic disorders. Implementing lyso Gb3 In diagnosis and follow-up of Fabry patients
  - Implementing analysis of alfa-aminoadipic acid in the diagnosis and follow-up of pyridoxine dependent convulsions (approved by the Belgian reimbursement authorities as a Reference Lab for this analysis in collaboration with the metabolic labs of UCL and Liege).
- **WP-6 Research** This SNW has undertaken several clinical studies with different sponsors:
  - Biomarin (sponsor): Fabry ERT new enzyme that can be given every 4 weeks (Bright study)
  - Amicus (sponsor): Pompe-adult combination therapy ERT + chaperone which enhances the availability of the enzyme for muscle tissue (in particular the skeleton muscle (ATB200-003 study)
  - Investigator-driven (Selective screening for Gaucher disease in patients with splenomegaly with/without thrombocytopenia

Carbohydrate, fatty acid oxidation and ketone bodies disorders (C-FAO)-Carlo Dionisi, Terry Derks, Ute Spiekerkötter

- **WP-2 Dissemination:** Coordinated by the UMCG, we are half way with our Priority Setting Partnership for liver glycogen storage diseases. For more information, see www.igsdpsp.com.
- **WP-4 Guidelines**: At the last board meeting it is decided to first concentrate on guidelines for VLCAD and MCAD deficiency. Contacted colleagues from the US who were in charge of the American VLCAD guideline (Southeast Regional Genetics Network) that is about to be published.
- The PoLiMeR (Polymers in the Liver: Metabolism and Regulation) consortium Horizon 2020 - Research and Innovation Framework Programme (call: H2020-MSCA-ITN-2018) proposal coordinated by prof. Barbara Bakker (UMCG) is awarded.

LSD- Ans van der Ploeg, Giancarlo Parenti, Dominique Germain

- **WP1: Coordination and Management**
- **WP2: Dissemination and Teaching activities** In the last months we dedicated lots of energy to the planning and organization of the Meeting of LSD subnetwork of MetabERN. The meeting will be held on Saturday November 3rd in Rotterdam, the Netherlands.

During the meeting we want to discuss several issues including:

- Update of the WPs (see what is there and where we are and see how we can help to get things done, see if we can do projects together
- Plans for Y3-Y5: what are the goals? What is needed?
- Ongoing projects relevant to the LSD subnetwork

- **WP4: Data Collection: Guidelines and Care Pathways and Standardisation, Transition:** we have started and defined a group of people that have signed up for the work GLs for some diseases on which we started. We are already using the platform developed by Ursula (selection and scoring of articles according to the instruction provided by the MetabERN WP4).

PM-MD- Shamima Rahman, Manuel Schiff, Enrico Bertini

This Subnetwork has approaching 20 active participants spread all over Europe and involved in the care of mitochondrial patients. Our activities for each of the work packages were as follows:

- **WP1: Coordination and Management**
  - Following the face-to-face meeting in Frankfurt, we have had a teleconference to discuss our activities. We plan to have more regular Webex meetings going forwards.
  - A survey has been distributed to all of the 69 MetabERN HCPs: big picture of the mitochondrial disease landscape in MetabERN: diagnostic investigations, number of patients, NGS etc.; also submitted to mito centres not within MetabERN (have reached out to ERN-EURO-NMD). Data analysis: pending – we are still awaiting the final data so that we can analyse these
- **WP2: Dissemination and Teaching activities**
  - ***Workshop in partnership with International Mito Patients (IMP) Patient Organisation:*** 1 November 2018, Amsterdam – Mitochondrial drugs workshop (SR will represent MetabERN Mito SNW)
  - ***Courses:***
    - 11-12 April 2019 in Nice (France): Recordati rare disease course on mito disease (in collaboration with MetabERN Mito SNW), chaired by SR with Pascal Laforet (adult neuromuscular, member of ERN-EURO-NMD)
    - 29-30 April 2019 SSIEM Academy, Zurich – will have a Mitochondrial theme (SR is lecturing for the last time, stepping down from ETAC after 12 years)
  - ***Publication:*** Mitochondrial disease paper from the Mitochondrial Medicine Society (Sumit Parikh, Amel Kara and Amy Goldstein, USA) was written and will be submitted soon. MetabERN is represented by the authorships of SR (last author), EB and MS
- **WP3: Evaluation**

The Spanish group are looking into this.

- **WP4: Data Collection: Guidelines and Care Pathways and Standardisation, Transition**

Daria Diodato and Diego Martienlli are working on this with Enrico Bertini.

- **WP5: Virtual Counselling**

CPMS for mito disease: we have been planning to organize at least 3 sessions per year. The first one should take place soon chaired by MS with Diego Martinelli

- **WP6: Research and Translational Activities, Clinical Trials**

We are in discussion about several clinical trials planned in Europe.

- **WP7: Capacity building and Training**

See activities for WP2 (courses)

- **WP8: Continuity of Care (prevention, treatment, follow-up)**

Niklas Darin (Sweden) and Rudy Van Coster (Belgium) are mapping mito diagnostic lab providers across Europe

Congenital disorders of glycosulation and disorders of intracellular trafficking (CDG)- Peter Witters, Pascale de Lonlay, Tomas Honzik

The names of the different representatives for the 9 Work Packages (WP) are the following:

WP-2	Dulce Quelhas, Gert Matthijs, Peter Witters
WP-5	Peter Witters
WP-6	David Cassiman, Dulce Quelhas,Gert Matthijs

WP-7	Pascale de Lonlay, Arnaud Bruneel

- **WP-4 Guidelines:** this Subnetwork (SNW) has a good overview of the guidelines that exist in their field. The second guideline this SNW will work on is on PMI-CDG. The first guideline drafted within this SNW is on PMM2-CDG guideline and is in the process of published).
- **WP-6 Research:** An overview on the research in the CDG-field can be found here:
- **Meeting**: The 1st French CDG-meeting with participation of the MetabERN leaders of the CDG Subnetwork is being prepared. It will take place on 22 March 2019.

Disorders of Neuromodulators and Other Small Molecules (NOMS) - Angeles Garcia Cazorla, Thomas Opladen, Eliane Sardh

- **WP-2 Dissemination:**
  - Networking meetings: I-NTD meeting in Athens, SSIEM, 3th September 2018
  - Dissemination activities: I-NTD newsletters have been sent out
- **WP-4 Guidelines**: this SNW has been working on BH4 defects, Porphyrias and Lesch-Nyhan
- **WP-6 Research:**
  - iPSc development for neurotransmitter defects, -omics studies for neurotransmitter defects, drug development in GLUT-1
  - Clinical trials (ADSL, BH4 deficiencies)
- **WP-7 Teaching courses:** "Inherited Vitamin Defects" (Recordati Rare Diseases Foundation), Paris, June 201

Patient Board

The names of the Single Points of Contact (SPOC) have been sent out to the WP-leaders and SNW-Coordinators in order to start communication and cooperation. The Steering Committee is working on its Action plan. The coming months they will be involved in teleconferences and meetings that will be organized. All Subnetworks and Work Packages have been encouraged to involve the Single Point of Contact and invite them to their teleconferences.