European network and registry for Homocystinurias and Methylation Defects (E-HOD)

Second Periodic Technical Report (April 2015)

1. EXECUTIVE SUMMARY (FOR PUBLIC DISSEMINATION)

Homocystinurias (HCU), methylation (MD) and folate defects (FD) are groups of rare chronic severe intoxication type inborn errors of metabolism (IEM) with overlapping phenotype. Individuals may present in infancy and are at risk of reduced quality of life and life expectancy. A major problem facing these rare diseases (RD) is that no single center, and in many cases no single country, has sufficient numbers of patients and resources to fully understand the natural history or to conduct clinical and translational research. There are no evidence-based guidelines and there are differences, between member states in infrastructure, expertise, time to diagnosis, treatment and outcome. In only five member states (MS) newborn screening (NBS) for HCU due to Cystathionine β-Synthase (CBS) deficiency is performed. Therefore the pooling of manpower and resources by establishment of a network and a registry is indispensable to improve the knowledge base, to develop European consensus guidelines, to foster networking on a European level and, ultimately, to promote health for patients with HCU, MD and FD.

SCOPE AND OBJECTIVES

The overall aim of the network and registry for homocystinurias and methylation defects (E-HOD) is to promote health for children, adolescents and adults affected with these rare and severe diseases. There are three specific objectives:

1) improving knowledge on homocystinurias (HCU) and methylation defects (MD) through the collection of clinical data into a registry,
2) developing diagnosis and clinical care recommendations,
3) evaluating the newborn screening (NBS) programmes and propose screening recommendations.

WORK ACHIEVED FROM 15th FEBUARY 2013 TO 14th FEBRUARY 2015 (1-24 MONTHS)

At the kick-off meeting (27th of February 2013), the consortium started with 32 partners (1 coordinator, 12 co-beneficiaries, and 19 collaborating) in 15 European countries and one Middle East Country (Qatar). At the end of the second project year the consortium is still growing and consists of 95 partners (1 coordinator, 12 co-beneficiaries, 75 collaborating, and 7 patients support groups, industry and other) in 28 countries on five continents (Europe, North America, South America, Asia and Australia). The network includes clinicians, scientists, dietitians, patient organisations and industry representatives. Representatives of other consortia have become members of E-HOD including those of the SSIEM adult metabolic group, the SSIEM dietitians' group thereby linking E-

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HOD with other organisations dedicated to improve health care for patients with rare homocystinurias and methylation disorders.

The first E-HOD advisory board meeting was a joint meeting with the E-IMD consortium held one day before the ICIEM 2013 in Barcelona. The **promotional leaflet** was printed in 2013 and has been distributed in the congress bags of the SSIEM 2013, the 9th International Conference on Homocysteine and One Carbon Metabolism (Dublin 2013) and to partners who have disseminated to national groups and people. This has increased the visibility of the EHOD project and the awareness for patients with HCU and Methylation defects.

The second E-HOD advisory board meeting was held in the Congress und Messe in Innsbruck, one day before the SSIEM 2014.

Forty-seven network members, Industry- and Patient Organizations representatives attended. The meeting afforded the occasion to review and evaluate the objectives and deliverables of E-HOD, better understand all stakeholders' perspectives and to discuss the work to be performed in the next 18,5 months.

Various other meetings (steering group, NBS and guideline groups) of consortium members were also held.

The next advisory board will be held 31st August 2015, one day before the SSIEM 2015 in Lyon.

The first version of the patient registry was launched in September 2013 (URL: https://www.ehod-registry.org). Since then monthly updates of the registry have been performed enabling ongoing optimisation of the IT solution.

The registry has achieved ethical approval of 43 centers and 312 patients have been registered.

E-HOD and OE are building Orphan Europe's post marketing registry ("Cystadane Surveillance Protocol", CSP) into the E-HOD registry through a public/private partnership.

63 CSP patients have been registered.

Between October 2013 and February 2015 the web-site has received 2, 800 visits, average time spent was 6 minutes, 53% visitors were new, 47% visitors were returning. The visitors were from all continents- see the map.

We receive requests for advice about individual patients and national patient groups. Contacts through the web are rapidly put in touch with one of our network members in the respective country or at least the requests are replied in the patient's own language. A combination of publications, web links and oral & poster presentations mentioning E-HOD has been initiated.

International guideline development groups have been set-up. Over 1000 publications have been searched and classified according to each group and subtopic. Partners evaluate each publication using a Monkey Survey questionnaire according to SIGN methodology. E-HOD has defined 4 groups for the guidelines:

1. Classical homocystinurias/CBS deficiency
2. Cobalamin defects
3. Methylation defects and other related disorders (MAT I/III, GNMT, SAHH, ADK)
4. Newborn screening evaluation group

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Draft statements have been established and reviewed by the groups. So far NBS guidelines recommendations have been published (give reference), Classical homocystinurias/CBS deficiency, Cobalamin defects and Methylation defects and other related disorders will be finished late 2015 or early 2016.

The project and its progress have been presented at international conferences including annual meetings of SSIEM, EUCERD, ICORD, VKS, CLIMB, REACT and EPIRARE.

The training courses on homocystinuria and methylation disorders will be extended: On 14th 2015 EHOD will organize an 0.5 day training on homocystinuria in a Recordati Rare Disease Advanced Course in Manchester. In early 2016 a full Recordati Rare Disease Advanced Course on Homocystinurias and Methylation Disorders will be held in Prague.

STRATEGIC RELEVANCE AND CONTRIBUTION TO THE HEALTH PROGRAMME

E-HOD adds value to the recent work and report on practices of newborn screening financed by the European Commission. The lead participants of this work will serve on E-HOD to evaluate the outcome of NBS for homocystinuria, which is screened for in 5 European countries and Qatar.

E-HOD is a network of leading scientists in the field; they are working in centres of expertise or are recognised as having the expertise. Therefore sustainability will most likely be sought through the national rare disease plans and impact of the European cross border directive. Furthermore, the registry will provide a unique source of data and will be an important tool for orphan drugs currently on the market or future treatments in development. This may also be a future source of sustainability.

By the end of the project it is hoped to have at least one network access point within each EU member state (MS). If it is not possible to set up a center in one country we will look at the feasibility of setting up a center for a group of countries. Given the particularly low number of patients and the complexity of the diseases, no national or regional project in Europe would be able to perform this work. The registry and network brings together physicians, care givers, scientists, patients and industry. The countries with fewer resources benefit from those with more resources i.e. access to consensus guidelines in their own language, diagnostic advice. It will map onto the evolving national rare disease plans and is complementary to existing rare disease networks. In accordance with the second Health Programme E-HOD promotes health, improves quality of life, and reduces health inequalities for patients with rare IMD. It provides best scientific evidence, empowers patients and their families and strengthens the community's status in the field of IMD.

CONCLUSIONS

E-HOD is performing exceptionally well and has achieved all milestones and deliverables for this second period. The project is innovative as it adds value to the reflection on EU Reference Networks and registries clustering 15 RD onto an existing network and registry (E-IMD) of 11 intoxication type diseases (E-IMD is funded by the EC EAHC 2010 12 01). It also adds value to the reflection on NBS programmes. Following the EMA/EUCERD discussions on the need to develop a unique source of data by disease, E-HOD leads the way in building a registry, with improved sustainability, for researchers, regulators, payers and for orphan drug follow-up through a strategy to develop

public/private partnerships. Given the particularly low number of patients and the complexity of the diseases, no national or regional project in Europe would be able to perform this work. It is complementary to and links to Orphanet. E-HOD maps onto the evolving national plans and strategies for rare diseases by ensuring that members of this group are centres of expertise or recognised for their expertise.

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