
**Joint Actions & Projects**
FINAL REPORT

# Call for Proposals 2008-2013

Executive Agency for
Health and Consumers

**SECTION I**

**Declaration by the scientific representative of the project coordinator**

**I, as scientific representative of the coordinator of this project and in line with the obligations stated in the Grant Agreement declare that:**

**X The attached periodic report represents an accurate description of the work carried out in this project for this reporting period;**

**The project (tick as appropriate):**

**X has fully achieved its objectives and technical goals for the period;**

**□ has achieved most of its objectives and technical goals for the period with relatively minor deviations.**

**□ has failed to achieve critical objectives and/or is not at all on schedule.**

**The public website, if applicable,**

**X is up to date**

**□ is not up to date**

**X To my best knowledge, the financial statements that are being submitted as part of this report are in line with the actual work carried out and are consistent with the report on the resources used for the project and, if applicable, with the certificate of the financial statement.**

**X All beneficiaries, in particular non-profit public bodies, have declared to have verified their legal status. Any changes have been reported under section wp1 Coordination and project management, in accordance with the requirements of the Grant Agreement.**

**Name of the scientific representative of the project Coordinator:**

**.....**

(Prof. Dr. Stefan Kölker, MD)

**Date: 12/08/2014**

**SECTION II**

## Checklist

**X the checklist has been filled, answered and printed. A printout is annexed to this report. An electronic copy is enclosed.**

**SECTION III**

**Specification of the project**

**Proposal title:** **2010 12 01**

**Acronym:** **E-IMD**

**Starting date:** **1 January 2011**

**Duration (in months):** **39**

**EC co-funding:** **720 071 €**

**Priority area:** **3.3.2 Promote health – Promote healthier ways of life and reduce major diseases and injuries**

**Sub-action:** **Rare diseases – support to creation of new registers on rare diseases**

**Action:** **3.3.2.7 Prevention of major and chronic diseases and rare diseases**

**Main partner information and contact person:**

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## Associated partner information and contact person:

| Acronym | Associated partner | Contact person |
|---|---|---|
| UZMS | Sveuciliste u Zagrebu, Mediciniski fakultet, Zagreb, Croatia | I. Baric |
| RH | Klinisk Genetisk Afdeling Rigshospitalet, Copenhagen, Denmark | A. M. Lund |
| CHRU L | Centre Hospitalier Régional et Universitaire de Lille, Lille, France | D. Dobbelaere |
| AP-HP | Assistance Publique Hôpitaux de Paris, Paris, France | V. Valayannopoulos |
| OE | Orphan Europe S.á.r.l., Paris, France | S. Parker |
| AZPD | Azienda Ospedaliera di Padova, Padova, Italy | A. Burlina |
| AMC | Academisch Medisch Centrum, Amsterdam, Netherlands | F. Wijburg |
| IPCZD | Instytut "Pomnik-Centrum Zdrowia Dziecka", Warsaw, Poland | J. Sykut-Cegielska |
| HSJ | Hospital de Sao Joao, EPE, Porto, Portugal | E. Leao Teles |
| CIBER | Centro de Investigación Biomédica En Red, Spain | A. Garcia-Cazorla |
| BCHNHSFT | Birmingham Children's Hospital NHS foundation trust, Birmingham, United Kingdom | A. Chakrapani |
| GOSH | Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom | S. Grünewald |

## List of collaborating partners:

### *1. CLINICAL PARTNERS (N=55)*

| Country | City | Contact person(s) | Organisation |
|---|---|---|---|
| Austria | Innsbruck | J. Zschocke | Medizinische Universität Innsbruck, Sektionen Humangenetik und Klin. Genetik |
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| Australia | Melbourne | A. Boneh | The Murdoch Childrens Research Institute, Royal Children's Hospital Melbourne |
| Belgium | Antwerp | F. Eyskens | Universitair Ziekenhuis Antwerpen |
| | Brussels | L. de Meirleir | University Hospital Vrije Universiteit Brussel, Department of Pediatric Neurology |
| | Brussels | E. Sokal | Cliniques Universitaire St Luc |
| | Brussels | C. de Laet | Hôpital Univ. des Enfants Reine Fabiola |
| | Gosselies | D. Roland | Center for Inherited Metabolic Diseases, Institute of Pathology and Genetics |
| | Liège | F.-G. Debray | Metabolic Unit – Dept. of Medical Genetics CHU Domaine Universitaire du Sart Tilman |
| Canada | Winnipeg | C. Greenberg | Depts of Pediatrics, Biochemistry and Medical Genetics, University of Manitoba |
| Czech Republic | Prague | J. Zeman, T. Honzik | Charles University of Prague, First Faculty of Medicine, Department of Pediatrics |
| France | Paris | H. Ogier de Baulny | Reference Centre for Metabolic Diseases, Hôpital Robert Debré, Université Paris VII |
| | Marseille | B. Chabrol | Reference Centre for Metabolic Diseases, Service de Neurologie, Hôpital d'Enfants, |

| | | | |
|---|---|---|---|
| | | | CHU Timone |
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| Germany | Düsseldorf | T. Meissner | Zentrum für Kinder- und Jugendmedizin, Universitätsklinikum Düsseldorf |
| | Freiburg | S. Grünert, U. Spiekerkoetter | Zentrum für Kinder- und Jugendmedizin, Universitätsklinikum Freiburg |
| | Hamburg | C. Mühlhausen | Klinik für Kinder- und Jugendmedizin, Universitäts-Klinikum Eppendorf |
| | München | R. Ensenauer | Dr. von Haunersches Kinderspital, Ludwig-Maximilian-Universität München |
| | Reutlingen | P. Freisinger | Klinik für Kinder- und Jugendmedizin, Klinikum Reutlingen |
| | Wiesbaden | R. Link | Representative, SSIEM Dietitians Group |
| Greece | Athens | E. Drogari | 1st Dept. of Paediatrics, University of Athens, Aghia Sophia Children's Hospital |
| | Thessaloniki | P. Augoustides-Savvopoulou | Thessaloniki University A'Pediatric Department-Metabolic Laboratory |
| India | Mumbai | A. Jalan | N.I.R.M.A.N., Om Rachna Society, Sector-17, Vashi, Navi Mumbai |
| Italy | Rome | C. Dionisi-Vici | Ospedale Pediatrico Bambino Gesù, U.O.C. Patologia Metabolica |
| Japan | Kumamoto | F. Endo | Dept. of Pedatrics, Kumamoto University Hospital (representative of J-UCDC) |
| Netherlands | Groningen | F.-J. van Spronsen | Children's Beatrix Hospital, University Medical Centre Groningen |
| | Rotterdam | M. Williams | Erasmus MC-Sophia Kinderziekenhuis, Erasmus Universiteit Rotterdam |
| Portugal | Lisbon | A. Gaspar | Unidade de Doenças Metabólicas, Serviço de Pediatria Hospital Santa Maria Lisboa |
| | Lisbon | I. Tavares de Almeida | Faculdade de Farmácia da Universidade de Lisboa |
| | Porto | L. Vilarinho | Newborn Screening Unit, Metabolic Genetics Center, National Institute of Health (INSA) |
| Romania | Bucharest | P. Avram | Institute for Mother and Child Care "Alfred Rusescu" |
| Serbia, Republic of | Belgrade | A. Sarajlija | Mother and Child Health Health Institute |
| Spain | Albacete | E. Balmaseda, C. Carrascosa | Complejo Hospitalario Universitario de Albacete |
| | Badalona | G. Pintos-Morell | University hospital "German Trias i Pujol" |
| | Barcelona | A. Ribes | Institut Bioquimica Clinica, Corpracio Sanitaria Clinic |
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| | El Palmar | I. Vives | Hospital Virgen de la Arrixaca de Murcia |

| | | | |
|---|---|---|---|
| | Granada | J. Maria de Haro Catellano | Secretaria Technica del CEI-Granada (HUVN), Edificio Licinio de la Fuente |
| | Las Palmas de Gran Canaria | L. Pena-Quintana | Hospital Univ. Materno-Infantil de Canarias, Universidad de Las Palmas de Gran Canaria |
| | Madrid | M. Ugarte, | Universidad Autonoma de Madrid |
| | | B. Merinero | |
| | Madrid | C. Pedrón-Giner | Sección de Gastroenterología y Nutrición, Hospital Infantil Universitario Niño Jesús |
| | Malaga | J. Blasco-Alonso | Hospital Materno-Infantil (HRU Carlos Haya) |
| | Palma de Mallorca | A. Ruiz Gómez | Hospital Universitario Son Espases |
| | Santiago de Compostela | M. L. Couce | Hospital Clinico Universitario de Santiago de Compostela |
| | Valencia | V. Rubio | Instituto de Biomedicina de Valencia |
| Switzerland | Zurich | M. Baumgartner, J. Häberle | Kinderspital Zürich, Universitäts-Kinderkliniken, Eleonoren-Stiftung |
| | Bern | J.-M. Nuoffer | Institute of Clinical Chemistry, Inselspital, Bern University Hospital |
| Taiwan | Taipei | W.-L. Wu | Department of Medical Genetics, National Taiwan University Hospital |
| Turkey | Istanbul | M. Demirkol | Istanbul University, Children's Hospital, Department of Nutrition and Metabolism |
| UK | Bradford | J. Walter | Bradford Teaching Hospital NHS Trust |
| | Manchester | J. Walter | Central Manchester and Manchester Children's University Hospital |
| | London | R. Lachmann | National Hospital for Neurology and Neurosurgery (representative of the SSIEM adult metabolic group) |
| | London | R. Vara | Dept. of Inherited Metabolic Disease, Evelina Children's Hospital, St Thomas' Hospital |
| USA | Pittsburgh | J. Vockley | Children's Hospital of Pittsburgh of UPMC |
| | Washington DC | M. Summar | Childrens National Medical Center (representing UCDC) |

### *2. PATIENT SUPPORT GROUPS (N=16)*

| Country | Contact person | Organisation |
|---|---|---|
| Belgium | L. de Baere | Belgische Organisatie voor Kinderen en Volwassenen met een Stofwisselingsziekte (BOKS) |
| Croatia | N. Caric | Hrvatska udruga za rijetke bolesti (Croatian Society for Rare Diseases) |
| Denmark | A. & K. Rovsing | Protein nedbrydningsdefekt foreningen (PND) |
| France | A. Kole | EURORDIS, Rare Disease in Europe |
| Germany | H. von Voss, R. Schmid | Kindernetzwerk e.V |
| | M. Kretschmer | Glutarazidurie e.V. |

| | | |
|---|---|---|
| Greece | P. Augoustides-Savvopoulou | Krikos Zois, Thessaloniki |
| | Z. Dimitroulis | PASIFASMEN - Hellenic association for patients with rare metabolic and endocrinologic diseases |
| Italy | R. Barbon Galluppi | UNIAMO FIMR |
| | S. Udina | COMETA ASMME - Associazione Studio Malattie Metaboliche Ereditarie - ONLUS |
| Netherlands | H. Meutgeert | Volwassenen en Kinderen met Stoffwisselingsziekten (VKS) |
| Portugal | V. Ferreira | Associação Portuguesa CDG |
| | M. Macedo | Apofen |
| | S. Braz Antão | Rarissimas |
| Spain | S. Faber | Catalana de Trastorns Metabòlics Hereditaris' |
| UK | S. Hannigan | CLIMB, Children Living with Inherited Metabolic Diseases |

### *3. INDUSTRY COLLABORATING PARTNERS (N=3)*

| Country | City | Contact person(s) | Organisation |
|---|---|---|---|
| Germany | Friedrichsdorf | M. Ott, B. Szczerbak | Milupa Metabolics |
| Germany | Heilbronn | P. Stäbe, B. Szczerbak | Nutricia |
| Sweden | Stockholm | S. Nordin | Sobi |

## FOREWORD

**This report aims** to review the main activities, challenges and solutions in establishing the European registry and network for intoxication type metabolic diseases (E-IMD).

Organic acidurias (OAD) and urea cycle defects (UCD) are two groups of rare, life-threatening, intoxication type metabolic diseases (IMD) with overlapping clinical phenotypes, predominantly presenting in infancy. As for many rare diseases, patients do not always have a specialist centre that they can attend where clinicians and other healthcare professionals, working as a multidisciplinary team, are experts in the particular disease. Furthermore, no single centre or often even a single country has sufficient numbers of patients and resources to fully understand the natural history or to conduct clinical and translational research. For example, for very rare diseases such as hyperammonemia-hyperornithinemia-homocitrullinuria (HHH) syndrome, carbamylphosphate synthetase 1 (CPS1) and arginase 1 (ARG1) deficiency, there are only about 3-4 births in Europe every year. As a result, care is not optimal; there are significant differences in the infrastructure, expertise, diagnostic procedures, time to diagnosis and outcome of patients. The pooling of manpower and resources through the setting up of E-IMD is a necessary area of collaboration.

**E-IMD is important** because it increases the scientific evidence base and knowledge by collecting information on rare diseases into a patient registry and by bringing together experts from national centres of expertise to work together at a European level. The patient registry provides a unique source of data for healthcare professionals, researchers, patients and policy makers to support decision-making. E-IMD has particular value as its consortium and IT structure have been built with the idea of gradually expanding to other IMD, using the same resources and thus producing economy of scale. E-IMD was launched with 11 intoxication type IMD; fifteen others (homocystinurias and methylation defects) were clustered from the EU-funded project "European network and registry for HOmocystinurias and methylation Defects - E-HOD" project (EAHC no. 2012 12 02) in 2013. Since the same year the IT platform has also been used for collecting follow-up data of patients receiving the orphan drug Cystadane™ (betaine anhydrous). This has been realised by a public private partnership between the drug license holder, Orphan Europe Sárl, and the E-HOD consortium. In 2014, a private grant has allowed for the addition of neurometabolic diseases ("International working group on NeuroTransmitter-related Disorders – iNTD"). As a next step, the IT platform is planned to be reutilised for the evaluation of health outcomes and quality of life of individuals with a metabolic and endocine disease identified by newborn screening. A grant application (acronym: EVALNBS) coordinated by UKL-HD has recently been invited to submit a full proposal for stage 2 of the evaluation within the Horizon 2020 call H2020-PHC-2014-two-stage. Clustering of single IMD and the development of an international network and flexible IT platform creates a unique opportunity for improving health of patients with rare inherited metabolic disease. This network is highly relevant in the reflection on European Reference Networks and the interoperability of registries.

**The key findings include:**

1/ Data from the registry have shown significant variation between countries in age at diagnosis, mode of diagnosis, diagnostic pathways and treatment. Since 2011, E-IMD has developed evidence-based recommendations (Kölker et al. J Inherit Metab Dis 2011; 34: 677-94; Häberle et al. Orphanet J Rare Dis 2012; 7: 32; Baumgartner et al. Orphanet J Rare Dis, accepted for publication). Adherence to these guidelines and their effect on the health outcome of affected individuals will be important to measure in the next years.

2/ Some OAD are included in the newborn screening (NBS) programmes in Member States or regions. The disease panel is different in each country and some countries do not screen (EAHC

service contract no. 2009 62 06). E-IMD has done some preliminary work to compare and evaluate NBS programmes, share protocols and expertise.

3/ Some countries are not able to offer patients optimal diagnosis and care, due to lack of expert centres or resources. The E-IMD network provides less experienced centres and individual clinicians with tools and advice. Furthermore, E-IMD provides specialised training to healthcare professionals from these countries. E-IMD has the capacity of implementing services related to the cross-border directive.

4/ The E-IMD survey to patients, conducted in 2012, has shown a need for up to date information about their disease and access to expert centres.

**The work from E-IMD is of benefit to:**

**1) Patients with OAD/UCD and their families:** They are confronted with significant inequalities due to lack of existing knowledge, low evidence base of divergent treatment strategies, and limited availability of understandable information. Giving access to information and consensus expert advice helps empower patients allowing them to better understand their disease; this helps establish optimal medical support. Ultimately this is a step towards equity of information and care throughout the EU.

**2) Patient support groups:** The process of interaction with national patient organisations will lead to improved dissemination of patient information. It may also lead to the establishment of novel patient groups in countries where none exist.

**3) Health care professionals (HCP):** Providing HCP with up-to-date information, consensus care protocols and training will lead to improved medical quality and networking.

**4) National and EU health authorities:** in sharing our processes, challenges and results we will support other rare disease networks. As a European reference network we are also in a strong position to provide authorities with important information and knowledge for any other matters concerning patient care for OAD and UCD.


## ACKNOWLEDGEMENTS

We are grateful for the support of:

- All patients and their families – for their important collaboration and trust in E-IMD.
- The European Union, in the framework of the Health Programme (2008-2013) for funding and support.
- Patient organisations that serve the network and give their time.
- SSIEM – for allowing us to organise the consortia meetings in Geneva (2011), Birmingham (2012) and Barcelona (2013) as a pre-meeting to the annual SSIEM (2011, 2012) and ICIEM (2013) meeting (within the same venue). This has helped to increase the visibility of E-IMD and awareness for intoxication type metabolic diseases.
- The Urea Cycle Disorders Consortium (UCDC) for starting transatlantic collaboration on urea cycle disorders.
- The Eurowilson network for kindly sharing the illustrations used in the brochures www.eurowilson.org.

## List of tables and figures.

**Tables**



**Figures**



## Keywords (using Mesh terms)

1. Rare disease
2. Metabolism, Inborn Errors
3. Registries
4. Guidelines
5. Evidence-Based Medicine

## SECTION IV

### Final Publishable Executive Summary.

**- A summary description of the project scope and objectives (general and specific).**

Organic acidurias (OAD) and urea cycle defects (UCD) are two groups of life threatening rare intoxication type metabolic diseases (IMD) with overlapping clinical phenotypes. The characteristics of rare diseases – a limited number of patients and scarcity of relevant knowledge and expertise – single them out as an area of especially high European added-value. The E-IMD project was funded from 1 January 2011 to 30 April 2014.

The overall aim of the European registry and network for Intoxication type Metabolic Diseases (E-IMD) is to promote health for individuals affected with rare OAD or UCD. E-IMD has two specific objectives:

(1) To establish a European patient registry describing the disease course, epidemiology, diagnostic and therapeutic strategies for OAD and UCD and to provide information to national and EU healthcare authorities. Anonymised data collection via a web-based password-protected EU registry will be based on routine follow-up parameters in 15 EU countries.

(2) To provide European evidence-based consensus care protocols for patients with OAD and UCD. Based on the largest available collection of patient data (see objective 1) and a systematic literature search, a European consensus group will describe the best evidence available for the diagnosis and treatment. Consensus care protocols will be translated into official EU languages, provided via the E-IMD website and serve as a template for national guidelines and patient brochures.

**- A description of the work achieved including methods and means.**

Within three years E-IMD has: (1) established a network of 87 partners in 25 countries; (2) set up a web-based patient registry (https://www.eimd-registry.org) with a cohort of more than 1,000 individuals with OAD and UCD registered; (3) launched a website (www.e-imd.org) including detailed information for patients in 11 languages; (4) developed guidelines for OAD and UCD; (5) organised six teaching courses and various scientific meetings; (6) extended the IT platform clustering with other inherited metabolic diseases (IMD); and (7) strengthened collaboration with other international scientific consortia.

The **network** was launched between 13 associated and 15 collaborating partners. Communication through the scientific societies, abstracts, presentations, patient organisations and the website has established the network legitimacy and spontaneous applications from new centres were made to the network. The network now includes 87 partners worldwide of which sixteen are patient organisations (PO). The governance structure is composed of a small steering group for day to day management and an advisory group of all members (Figure 1). The advisory group meets annually.

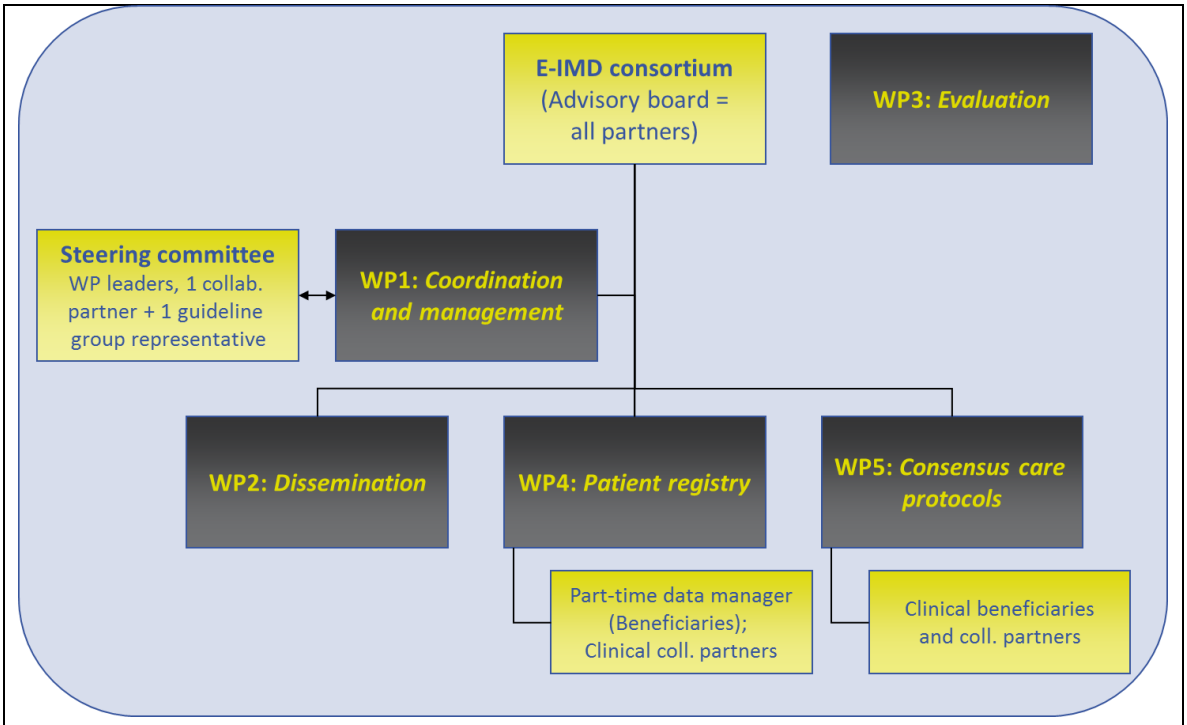


**Figure 1. Governance structure of E-IMD**

The E-IMD **patient registry** is web-based and password-protected (https://www.eimd-registry.org). It contains comprehensive information on patients with a confirmed diagnosis of OAD and UCD. Written informed consent is obtained from all study patients before enrolment and baseline visit. The study was approved by the local ethics committee of the coordinating centre and then approved by the ethics committees of clinical partners contributing to the registry (n=44). Each associate partner recruited a data manager. Some associate partners managed to record all or most cases in their country, whilst other centres may only have reached a regional coverage (particularly collaborating partners). We note that Switzerland, Czech Republic and Austria have performed remarkably well despite their collaborating partner status and lack of funding from the Commission. As of 30 April 2014, 1009 OAD and UCD patients have been registered.

**Guidelines** were developed for UCD, isovaleric acidurias (IVA), methylmalonic aciduria (MMA)/ propionic acidurias (PA) and glutaric aciduria type 1 (GA1). A guideline is defined as a systematically developed statement that assists practitioners and patients decisions in appropriate healthcare for specific clinical circumstances. They are of particular value to provide recommendations in clinical situations where variations in practice are known to occur and where effective care may not be delivered uniformly. Their overall aim is to improve the outcome of patients. They also help improve awareness. For E-IMD, each group defined topic groups, i.e. diagnosis, treatment, complications, transplantation, outcome etc. and key questions, i.e. *What drugs to use?*, *What diagnostic strategy to chose?*, etc. The methodology is a nominal group process using the AGREE instrument. Each group has a coordinator, 2 moderators, secretary, external consultants and reviewers. The group use the literature scoring evidence level system from SIGN. A systematic literature review and grading using SIGN levels of evidence was performed. Most of the metabolic literature is in the range of 4 (expert opinion), 3 (case reports) or rarely $2^+$ (case control or cohort study). Then recommendations are graded according to levels of evidence. The aim is that recommendations are executable, specific and concrete. The statements should say: *Who should do what, to whom, when, how and why?* For example, the MMA group evaluated over 350 papers and selected 220 of particular relevance. At the end they developed 69 statements. These guidelines serve as templates for validation by national scientific societies/member states.

**- The final results in terms of outputs and outcomes, and their potential impact and use by the target group (including benefits).**

This work has resulted in several areas of added value to the IMD and RD community:

a) *Development of an international network for collaboration, sharing knowledge, evidence and experience:* During the project, the number of centres applying for participation steadily increased to European countries that were not initially part of E-IMD and non-European partners (Figure 2). The network has demanded close collaboration between clinicians, diagnostic laboratories, scientists, patients and their families. The network serves as a centre for information, research and knowledge; updating and contributing to the latest scientific findings, and proposing the best strategies for managing patients.

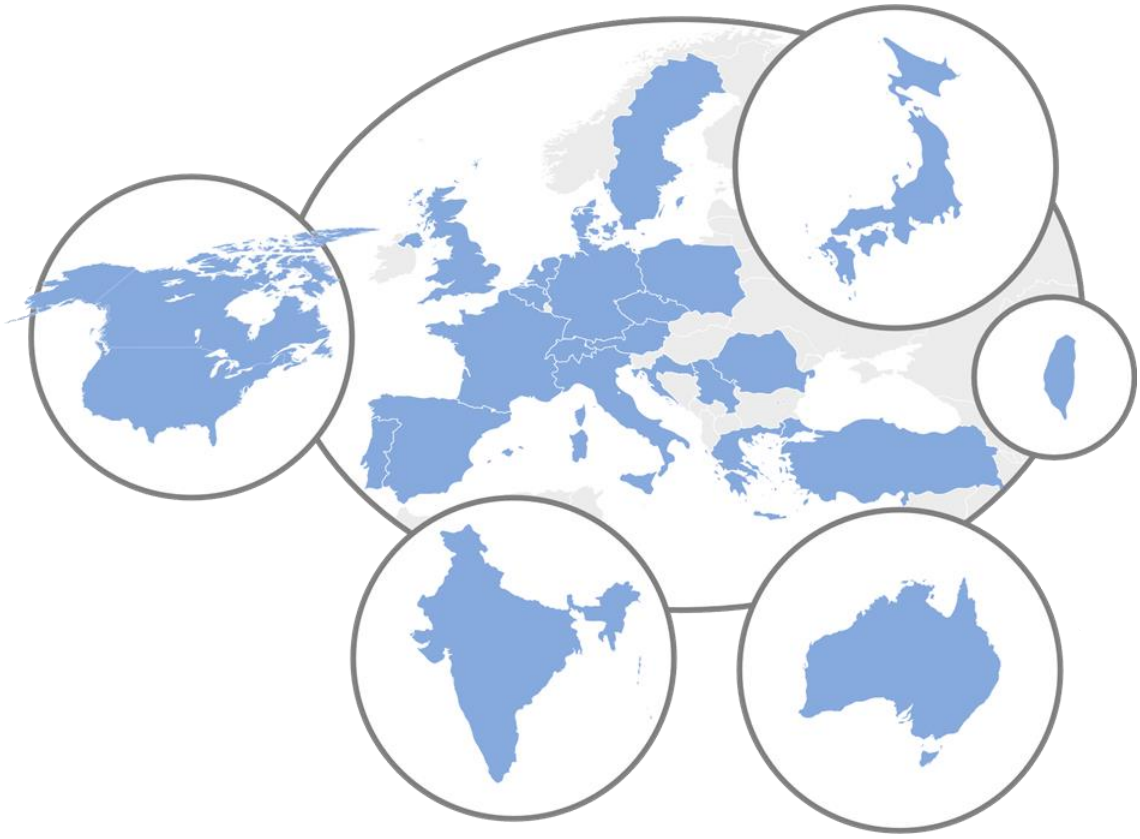

**Figure 2. The E-IMD network.** So far, 87 partners from 25 countries on 4 continents are included. Note that the coloured areas do not reflect the exact geographical coverage of E-IMD.

b) *Development of diagnostic and clinical guidelines:* The development, translating and dissemination of evidence-based best practice guidelines for diagnosis and management have been a core activity. Four guideline papers have been produced and shortened versions are in the process of translation. They include the provision of recommendations for effective practice in clinical situations where variations are known to occur and where effective care may not be delivered uniformly.

c) *Development of an international registry for OAD and UCD:* The registry plays an important role in auditing current care, improving knowledge and providing standards to reduce variation and improve patient outcome. Data from the registry have been and will be

published in peer-reviewed journals focusing on the precise description of the clinical phenotype and its development from the newborn period to adulthood, evaluation of quality of life, cognitive development and behavioural problems, and the effect of varying diagnostic and therapeutic strategies on the health outcome.

d) *Expansion of the disease panel to homocystinurias and methylation defects:* In 2013, homocystinurias and methylation defects were added to the network by achieving funding for the E-HOD project (EAHC grant no. 2012 12 02). In 2014 neurometabolic disorders (iTND, Dietmar Hopp Foundation) are being added to make a total of 50 diseases followed by the network.

e) *Development of a Federation of patient organisations:* Surveys of patient groups identified a need for closer working and exploring areas of mutual interest such as setting up a patient federation of inborn errors of metabolism organizations. The initial steps have been taken, as indicated by the establishment of the European Metabolic Disorders Alliance (EMDA) www.eumda.org.

f) *Communications and infrastructure to ensure visibility and accessibility*: Members of the network publish and present data from the network on a regular basis – the communication is essential to ensure that patients and non-experts find the network

g) *Collaboration with industry*: the pharmaceutical and services industry is interested in the outputs of E-IMD and access to knowledge, natural history data, orphan drug research and development including post marketing safety surveillance. E-IMD has set up an efficient system for encouraging collaboration with the industry. As a first result of the interaction with the industry, E-HOD which builds upon E-IMD has been established a public private partnership with Orphan Europe in order to collect follow-up information on patients receiving the orphan drug Cystadane™ (betaine anhydrous). In addition, E-IMD members collaborate with another orphan drug company which plans an interventional trial on a new orphan drug for UCD patients in Europe.

h) *Research*: Deep phenotyping of patients with rare diseases using systematic collection of comprehensive clinical follow-up parameter in a patient registry is a major prerequisite for successful translational medicine. It helps to predict the severity of the clinical phenotype of individual patients. This is the basis for stratifying and individualizing treatment and care. Members of the E-IMD consortium have also investigated the pathophysiology of OAD and UCD and have tested new therapeutic strategies using cell cultures, animal models, etc. These projects have been funded by other sources. This interdisciplinary approach shall be the basis of innovation for patients with rare diseases such as the development of new drugs and optimized treatment and care strategies, and shall reduce the time required to implement innovations into daily practice.

**- The strategic relevance and contribution to the Health Programme.**

**E-IMD is important** because it increases the scientific evidence base and knowledge by collecting information on rare diseases into a patient registry and by bringing together experts from national centres of expertise to work together at a European level. The patient registry provides a unique source of data for healthcare professionals, researchers, patients and policy makers to support decision-making. E-IMD has particular value as its consortium and IT

structure have been built with the idea of gradually expanding to other IMD, using the same resources and thus producing economy of scale. E-IMD was launched with 11 intoxication type IMD. Fifteen others (homocystinurias and methylation defects) were clustered from the E-HOD project (EAHC no 2012 12 02) in 2013. In 2014, a private grant has allowed for the addition of neurometabolic diseases. Clustering of single IMD and the development of an international network and flexible IT platform creates a unique opportunity for improving health of patients with rare inherited metabolic disease. This network is highly relevant in the reflection on European Reference Networks and the interoperability of registries. A grant application (acronym: EVALNBS) coordinated by UKL-HD has recently been invited to submit a full proposal for stage 2 of the evaluation within the Horizon 2020 call *H2020-PHC-2014-two-stage*.

**- Conclusions and recommendations.**

E-IMD is highly successful in its objective of improving healthcare for patients with OAD and UCD and their families wherever they live in Europe. The network of participating centres of expertise is large and partners enthusiastically embrace the principles of widening access to and improving quality of diagnostic and clinical services. Information for patients, families and non-expert clinicians is available in a large variety of European languages. The establishment of the European registry is a major step forward in understanding some of the very complex clinical and biochemical issues related to OAD and UCD. The guidelines provide standards for improving the care of patients and decreasing variability. The network has engendered a momentum and enthusiasm among professionals working in this field to continue and build on what has been achieved so far – this is a good indicator that the network can be sustained through the understanding that collaboration is required in these rare diseases. However, without European funding the network will work with reduced activity. This will inevitably imply that less developed countries or structures will be most disadvantaged when having to find national or local funding.

There is a key role of Member States to endorse and approve this type of a network. A recommendation would be for healthcare structures to reduce the administrative burdens for centres of expertise to participate in a network and registry by providing staff for ethical approval, data entry and covering costs and time for experts to attend meetings.

All members of E-IMD feel very strongly that the network and registry must continue and that we should apply for European Reference Network status through the future call of interest.

## SECTION V

## Technical aspects of the project

### Background and project scope

Estimated incidences of single OAD and UCD are thought to be in the range of 1 in 15,000-200,000 newborns resulting in an estimated cumulative incidence of 1 in 5,000-10,000 newborns in the EU. Affected individuals with these life-threatening diseases predominantly present in infancy and are at an increased risk of severe disability, impaired quality of life, and reduced life expectancy. These patients have become a healthcare priority in developed countries where other causes of infant mortality such as infectious diseases are now treatable. However, because these diseases are rare, single centres or countries base patient care on their own, often very limited, experience. As a result, care is not optimal, and there are significant differences in the infrastructure, expertise, diagnostic procedures and time to diagnosis, strategies and outcome. This causes significant inequalities and inequities for patients with OAD and UCD and, consequently, has a significant impact on their outcome and health as well as on the socio-economics of European countries. In some European countries networking activities exist on a national or regional level, and national plans or strategies for rare IMD, and rare disease in general, start to evolve, whereas other countries still have a considerable lack of infrastructure and expertise for rare IMD. Therefore a registry for rare OAD and UCD 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 OAD and UCD in Europe. It is evident from previous work at a national level that these measures can positively influence the natural disease course of OAD and UCD.

### General objective of the project

The overall aim of the European registry and network for Intoxication type Metabolic Diseases (E-IMD) is to promote health for individuals affected with rare OAD or UCD. E-IMD has two specific objectives:

(1) To establish a European patient registry describing the disease course, epidemiology, diagnostic and therapeutic strategies for OAD and UCD and to provide information to national and EU healthcare authorities. Anonymised data collection via a web-based password-protected EU registry will be based on routine follow-up parameters in 15 EU countries.

(2) To provide European evidence-based consensus care protocols for patients with OAD and UCD. Based on the largest available collection of patient data (see objective 1) and a systematic literature search, a European consensus group will describe the best evidence available for the diagnosis and treatment. Consensus care protocols will be translated into official EU languages, provided via the E-IMD website and serve as a template for national guidelines and patient brochures.

## Specific objective(s) of the project

### Table 1. E-IMD objectives

| | Title and Description | Link to the WPs<br><br>(table 2) | Link to the deliverables (table 2) | Level of achievement (measured by the indicators specified in WP3) |
|---|---|---|---|---|
| **1** | European patient registry to describe the natural history, epidemiology, and current diagnostic and therapeutic strategies for rare OAD and UCD and to provide information to national and EU healthcare authorities | 1 | 6 | Process indicators:<br>• Items to be included in the registry for data collection have been agreed on before programming the registry. The E-IMD registry has been online since M7. The IT system is modular and flexible allowing future adaptation such as inclusion of new items if necessary. The publicly visible part of the registry is available online at https://www.eimd-registry.org (*full achievement*).<br>• Quality and completeness of records in the database is analysed on different levels. Internal validation tools help to improve the quality and completeness in real-time mode. Monthly data quality reports are sent to partners by UKL-HD (*full achievement*).<br>Output indicator:<br>• Number of cases in the registry are reported in real-time mode on the publicly visible part of the registry specifying numbers of patients per centre and country. Number of cases exceeded expectations, 168% (i.e. datasets of 1009 patients) of the minimal project goal has been achieved (*full achievement*).<br>Outcomes indicator:<br>• During the course of the activity consensus care protocols for OAD and UCD have been developed and published. All E-IMD partners have |

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|---|---|---|---|---|
| | | | | agreed on using these recommendations and to translate them into national guidelines. This is a time-consuming process and will be continued after the project period. The effect of these changes on the long-term outcome, however, cannot be realibly estimated at the end of the funding period. A longer follow-up time would be required to evaluate this effect longitudinally. A cross-sectional analysis, however, has been performed evaluating different diagnostic and therapeutic strategies. In addition, pilot studies on the use and usefulness of guideline recommendations have shown that acceptance and use of guidelines have been excellent and that the use of treatment recommendations has improved the short-term health outcome (shown for GA1) (*full achievement*). |
| **2** | To provide European evidence-based consensus care protocols for OAD and UCD | 2 | 9 | Process indicators:<br>• Website contents have been agreed by the consortium. The website is accessible online at http://www.e-imd.org (*full achievement*).<br>• Annual consortium meetings have been held on schedule, steering group meetings have been held regularly, additional meetings such as with PO groups and guideline groups have been organised. SIGN methods have been used during 14 guideline group meetings in order to develop consensus care protocols (*full achievement*).<br>Output indicators:<br>• The website has achieved good coverage and accesses have been made worldwide. About 200 accesses to the website per month have been documented on average from January 2012 to April 2014 (see also figure 8 in the evaluation report, i.e. deliverable #10). On average, users stayed 6-7 minutes on the website. The website has been an important instrument for patients and external healthcare professionals to contact the network. The main enquiries are related to the location of an expert in a particular country, advice on care / treatment, future research. All |

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| | | | | enquiries are answered in a timely manner, to the greatest extent possible, in the individuals own language. The google search engine lists the E-IMD website on the first page when typing “organic aciduria” or “urea cycle disorder” (*full achievement*).<br>• Two consensus care protocols have been published (GA1, UCD), one has recently been accepted for publication (MMA/PA), and another will be submitted for publication in 2014. Brief versions (quick reference guides) are available for all E-IMD diseases on the E-IMD website, i.e. for GA1, MMA/PA, IVA, and UCDs. Information brochures for patients, parents, and healthcare professionals have been developed. Brochures for healthcare professionals are in English, whereas brochures for patients and parents have been translated into 11 languages and made available via the website (*full achievement*).<br>Outcomes indicator:<br>• All E-IMD consortium members use E-IMD recommendations for OAD and UCD (*full achievement*). |

## Overview of the workpage and deliverables:

### Table 2. Work packages (WP) and deliverables (D)

| WP | WP Title | Deliverables | Description | Confidentiality | Expected month of delivery (according to amendment 1) | Actual delivery month | Comment |
|---|---|---|---|---|---|---|---|
| **1** | **Coordination of the project** | D3 | Interim report 1 | Public | 12 | 14 | This is in time according to the grant agreement. |
| | | D4 | Interim report 2 | Public | 24 | 26 | This is in time according to the grant agreement. |
| | | D7 | Annual meetings | Public | 33 | 33 | M8 (Geneva), M21 (Birmingham), M33 (Barcelona) |
| | | D8 | Final report | Public | 40 | 43 | |
| **2** | **Dissemination of the project** | D1 | E-IMD promotional leaflet (print and electronic version) | Public | 3 | 5 | |
| | | D2 | Launch website and electronic newsletter | Public | 5 | 8 | |
| | | D5 | Training course (Orphan Europe Academy) | Scientif. community only | 27 | 14 | Six training courses have been organised in collaboration with the Orphan Europe Academy (now known as the Recordati Rare Disease Foundation ) : |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | 1/Neurological manifestations of metabolic disorders from paediatrics to adults<br>2/E-learning hyperammonemia module<br>3/1st Advanced Meeting on metabolic and genetic disorders affecting the Liver, Rome Italy, 28-30 March 2012<br>4/Inherited metabolic diseases for the internist, Amsterdam, 6-8 June 2012<br>5/European inborn errors of metabolism general course, Warsaw, Poland 25-29 September 2012<br>6/Behavioural and psychiatric aspects of inborn errors of metabolism, Paris, France, 23-24 May 2013 |
| **3** | **Evaluation of the project** | D10 | Evaluation of process and outcome indicators | Public | 40 | 43 | Evaluation report submitted with final report |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **4** | **European patient registry** | D6 | European patient registry of OAD and UCD cases | Confidential | 33 | 33 | We have continued to register and follow patients until the end of the funding period (M40). |
| **5** | **Consensus care protocol** | D9 | Consensus care protocols and information brochures | Public | 40 | 40 | UCD and GA1 recommendations have been published, the MMA/PA have been accepted for publication (MMA/PA), IVA recommendations are expected to be published by the end of 2014. |

**Main activities carried out including methods and means.**

*Coordination*

The project is managed by the Coordinator (UKL-HD) with support from OE. A kick-off meeting (Luxembourg 01-02 February 2011) and three annual advisory board meetings (Geneva 29-30 August 2011, Birmingham 3-4 September 2012, Barcelona 1 September 2013), nine steering group meetings (Paris 23 May 2011, Geneva 29 August 2011, Zurich 17 November 2011, Paris 16 Jan 2012, Paris 10 May 2012, Birmingham 2 September 2012, Paris 25 April 2013, Paris 19 July 2013, Barcelona 1 Sept 2013), and 14 meetings of guidelines groups have occurred. In addition, the international FoNM 2012 symposium on *"Approaching the 'deep' metabolic compartment"* (Fulda 17-19 October 2012, in collaboration with Nutricia) and an international satellite meeting of the ICIEM 2013 symposium on *"Catalyzing new therapeutic approaches"* (Barcelona 1-2 September 2013, in collaboration with the Urea Cycle Disorders Consortium and the National Urea Cycle Disorders Foundation) were co-organized by the Coordinator and other E-IMD consortium members. Communication and day-to-day management of the consortium has been performed by e-mail and telephone. Meetings between the WP1 leader and the financial department of the coordinator took place quarterly. Partners were informed in detail and in time about the requirements for annual technical and financial reporting by the WP1 leader.

*Development of an international network for collaboration, sharing knowledge and experience*

The network started with the coordinator, 12 associated partners and 15 collaborating partners in 15 European countries. The network has grown beyond expectations to a group of 87 partners (74 collaborating) in 25 countries and 4 continents (Europe, North America, Australia, and Asia). The network includes clinicians, scientists, dietitians, patient organisations and industry representatives. Representatives of other consortia have become members of E-IMD including those of the SSIEM adult metabolic group, the SSIEM dietitians' group, the USA Urea Cycle Disorders Consortium (UCDC) and the Japanese Urea Cycle Disorders Consortium (J-UCDC) thereby linking E-IMD with other networks dedicating their efforts to improved health for patients with rare UCD and OAD.

*Development of a Federation of patient organisations*

Surveys of patient groups identified a need for closer working and exploring areas of mutual interest such as setting up a patient federation of inborn errors of metabolism organizations. The initial steps have been taken, as indicated by the establishment of the European Metabolic Disorders Alliance (EMDA) www.eumda.org.

*Dissemination*

A promotional leaflet with the E-IMD logo describing the composition of the study consortium, the activities and time schedule of E-IMD has been circulated among the E-IMD partners, all European metabolic centres and relevant stakeholders in M5.

The website has been online since M8. We received over 7000 annual visitors from September 2011 – April 2014. The patient information are the most frequently visited pages. We receive requests for advice about individual patients. Contacts through the web are rapidly put in touch with one of our network members in that country or at least the requests are replied in the patient's own language.

A combination of publications, weblinks and oral and poster presentations mentioning E-IMD has been produced and presentated. Six publication projects have been identified for the interim analysis of the patient registry, additional publication projects will be realised after the end of the funding period. Two guideline recommendations have been published in peer-reviewed journals and on the web, the publication process of two other guideline

recommendations is ongoing and expected to be finalized in 2014. Based on guideline recommendations, brochures for patients and their families as well as for families have been produced and translated into 11 languages. They are available online via the website.

*Evaluation*

As part of the evaluation processes two surveys were undertaken. The surveys were coordinated by CLIMB (www.climb.org.uk). The survey was put on the website to a larger public. The achievement of process, output and outcomes indicators have been systematically evaluated according to the evaluation plan. E-IMD has achieved all major goals and has often gone beyond expectations: For example, the network has become a true international effort, more training courses have been organized and more patients registered than planned. An evaluation report has been produced describing the evaluation methodology, results, conclusions and recommendations.

*Development of an international patient registry for OAD and UCD*

The patient registry contains a set of common data elements for all OAD and UCD patients as well as a set of parameters that is tailored to the requirements of specific disease (e.g. biomarkers). The following data is collected:

- Diagnostic process including detailed clinical, biochemical, molecular and enzymatic parameters confirming the suspected diagnosis as well as documenting the time of the diagnostic process.
- Medical history including detailed information on the first clinical symptoms of the disease and the age at disease onset as well as significant co-morbidities such as preterm infancy, etc.
- Physical and neurological examination and evaluation of the physical and neurological development. To evaluate the disease course and severity in patients from different partner countries the ICD-10 code is used to specify every diagnosis of an individual patient.
- Detailed follow-up information on therapy protocols including dietary treatment and pharmacotherapy. The use of licensed orphan drugs in partner countries is specifically monitored.
- Test results of neuropsychological evaluation such as Bayley Scales of Infant Development and age-adapted Wechsler tests for IQ assessment.
- Behavioral abnormalities and their effects on family life are assessed by a (patient and parent) questionnaire which has been developed for this registry.
- Quality of life assessment using standard tools such as the PedsQL questionnaire for children and their parents as well as the WHOQOL-BREF for adults.
- Follow-up of patients is completed by key biochemical (routine laboratory and specific metabolic) parameters and MRI findings.
- For emergency visits, putative triggers precipitating metabolic crises, management of emergency treatment and outcome is evaluated in addition to standard clinical and biochemical parameters.
- In patients with fatal disease course, the (suspected) cause of death is documented.

An item list with all above mentioned baseline and follow-up parameters has first been agreed by all consortium members. Special attention was made to the availability, comparability and

harmonisation of all follow-up parameters, in particular those differing in partner countries such as various tools for neuropsychological assessment and quality of life assessment. After harmonisation of the item list, the E-IMD patient registry has been programmed (starting in M4). Subsequently, tests with virtual and real probands have been performed by the UKL-HD team before the first version of the patient registry was launched in M7 (URL: https://www.eimd-registry.org). Since then monthly updates of the registry have been performed enabling ongoing optimisation of the IT solution. Optimal data quality and completeness of the dataset is achieved by internal validation tools and monthly reports to individual partners provided by UKL-HD. Numbers of patients by centre and country are available to the public in real-time mode, whereas the pseudonymized detailed dataset is accessible only for clinical E-IMD partners.

The database is hosted by UKL-HD, and an APACHE server is used for data storage. Hypertext transfer protocol secure (HTTPS) enables encrypted communication and secure identification of the network web server. Daily backups are performed and stored for 30 days; all data are also mirrored to another server located in another building. A MySQL database and TYPO3 software, an open source content management system, is used. Access to the patient registry is protected by password. The precondition to receive personalised access codes is: (a) authorisation of the data manager by individual partners, and (b) ethics approval of individual partners. Entry of patient data is started after written informed consent has been obtained. All entered data are pseudonymised. Individual partners only receive access to data of patients followed by their own centre. Each partner has the opportunity to download centre-specific patient data as a .csv file and to print out pseudonymised visit data.

Approval by the UKL-HD research ethics committee was obtained in January 2011. UKL-HD has given support to other partners providing a template for the ethics application, patient and parent information, and informed consent forms in English language in February 2011. As OAD and UCD affect children, adolescents and adults, information sheets and consent forms were needed for children, parents, and adults. Specific reference was also made to consent issues in adults with impaired cognitive ability.

Translation of the ethics template in other languages, adaptation to the requirements of individual centres and countries and the external evaluation process have been time-consuming. Furthermore, a significant difference in the duration of this process in European countries has been identified. By M40, 44 partners in 22 countries have received ethics approval.

From the start of the project until 30 April 2014, 1009 patients with confirmed diagnosis of an OAD or UCD have been registered. This is 168% of the minimal project goal. A total of 929 baseline visits, 1072 annual follow-up visits, 413 emergency visits, and 14 fatal disease course visits have been performed, i.e. 2.41 visits per patient on average.

*Expansion of the disease panel to homocystinurias and methylation defects*

In 2013 homocystinurias and methylation defects were added to the network by achieving funding for the E-HOD project (EAHC grant no. 2012 12 02). In 2014, neurometabolic disorders (iTND, Dietmar Hopp Foundation) have been added to make a total of 50 inherited metabolic diseases followed by the network.

*Guideline development*

Guidelines for OAD and UCD was developed by four groups of experts, i.e. for UCD, GA1, MMA/PA and IVA. Guideline development was performed following the SIGN methodology. In brief, this includes the establishment of a group of experts (including PO representatives), identification of guideline topics, systematic literature review of relevant publications, evaluation of published evidence, formal consensus finding, formulation of recommendations and specifying the strength of the recommendation, external review and publication. At least

three meeting per group have been performed during the course of the activity. So far the revised GA1 guideline and the UCD guideline have been published. Recommendations for PA/MMA have recently been accepted for publication. IVA recommendations have been formulated; their publication process will be finalised in the second half of 2014.

### Target groups

**1) Patients with OAD and UCD and their families:** They are confronted with significant inequalities due to lack of existing knowledge, low evidence base of divergent treatment strategies, and limited availability of understandable information. Giving access to information and consensus expert advice helps empower patients allowing them to better understand their disease; this helps establish optimal medical support. Ultimately this is a step towards equity of information and care throughout the EU. Information on 1009 patients has been collected in the patient registry until M40. Positive feedback from individual patients and their families has been given for the provision of detailed information brochures in different European languages.

**2) Patient support groups:** The process of interaction with national patient organisations has led to improved dissemination of patient information. The interaction between PO groups and E-IMD has resulted in the establishment of the European Metabolic Disorders Alliance (EMDA, www.eumda.org) which supports families, young people, adults and professionals throughout Europe who are affected an IMD. E-IMD has worked with EURORDIS (see WP3) and has involved patient groups in a project advisory role (several associations are aware of this project). Patient support groups from 10 European countries and EURORDIS (see also: Section III) have become partners of the E-IMD consortium. They have been actively involved in the establishment of the item list for the patient registry, the development of the website, the patient survey, organisation of consortium meetings, and guideline development.

**3) Health care professionals (HCP):** Providing HCP with up-to-date information, consensus care protocols and standardised training has led to improved medical quality and networking with experts and stakeholders.

**4) National and EU health authorities:** Rare diseases and the gathering of expertise at a European level are an EU Priority. The EU recommends the setting up of national rare disease plans or strategies in all MS by 2013. E-IMD is completely complementary. Information about E-IMD progress has been given to EUCERD to assist with their decision-making and policy priorities.

### Evaluation of the degree of achievement of the objectives and discussion based on the project's indicators as outlined in your evaluation plan/ WP3.

E-IMD has fully achieved all major goals and deliverables as specified in Annex Ia. This can be proven by the evaluation of project's specific indicators (see below).

**Process indicators for specific objective 1:**

(1) Agreed items to be included in the registry for data collection: this has been achieved by March 2011 (M3), i.e. before the start of programming the patient registry. Optimisation and tool harmonisation has been continued during the course of the project to further improve the IT solution. The flexible IT allows adaptation of the registry and thus inclusion of new parameters and diseases.

(2) Number of cases reported in the registry by country/centre: In general, 1009 patients have been registered. This is 168% of the expected minimal number of patients to be recruited during the course of the project. Centre-specific differences reflect discrepancies in the timeline

of partners to receive ethics approval, employ data managers, and start patient recruitment rather than true differences in prevalence per country. We have observed a significant difference in the activity of associated and collaborating partners, with associated partners having entered about 75% of the patient data.

(3) Number of patients participating in quality of life survey (PedsQL, WHOQOL-BREF survey) and measurement of disability survey: QoL assessment is not included as a mandatory task for the enrolment and baseline visit. Therefore, collection of QoL data has not been started before 2012, i.e. after the start of regular (annual) follow-up visits. We have received 126 QoL questionnaires as well as self and parent reports assessing the behaviour of patients with UCD and OAD. As an additional project, we have started to develop a health-related QoL for children and adolescents with intoxication type metabolic diseases.

**Outcome indicators for specific objective 1:**

(1) Analysis report on differences in diagnosis, treatment and outcome: The development of a concise statistical strategy has started in 2012 and finalised in 2014. A scientific biostatistics manager has been employed at UKL-HD at 01 Jan, 2012. Six publication projects have been identified with a focus on a precise description of the natural phenotype, the identification of age-specific complications, genotype phenotype correlation, the identification of variant disease courses, the comparison of different diagnostic and therapeutic strategies on the health outcome of OAD and UCD patients, and on behavioural abnormalities and QoL. Interim analysis has been performed in a dataset using 22 October 2013 as the cut-off date.

(2) Compliance to guidelines: All E-IMD partners have agreed to use the recommendations developed for OAD and UCD during the course of the activity. To evaluate the effect of using these recommendations longitudinally, however, can only be evaluated reliably after a follow-up period of more than three years. First pilot studies on the use and usefulness of UCD and GA1 guidelines have shown very promising results.

**Process indicator for specific objective 2:**

(1) Number of hits, unique visitors and enquiries to the E-IMD website

The website has received nearly 7000 annual unique visitors from September 2011 – April 2014. Visitors spent an average of 6-7 minutes on the website.

**Outcome indicators for specific objective 2:**

(1) Number of existing recommendations in Europe for OAD and UCD:

As an important result, the E-IMD consortium has published three consensus care protocols for patients with UCDs, GA1, MMA/PA. The guideline recommendations for IVA have also been formulated and will be submitted for publication by the end of 2014. Detailed analysis of existing recommendations for OAD and UCD at the start of E-IMD is provided in the report on WP5.

(2) Number of EU metabolic centres using evidence-based recommendations for OAD and UCD:

See above: guidelines have been developed during the course of the project. Two consensus care protocols for UCDs and GA1 have already been published, the third for MMA/PA has been accepted for publication, recommendations for IVA have been formulated and are expected to be published by the end of 2014. These recommendations are used by all E-IMD partners.

(3) Consensus care protocols for OAD and UCD available on E-IMD website in main European languages:

Full guidelines are published in English in peer-reviewed journals, short versions are published in English on the E-IMD website. Based on these recommendations brochures for patients and their families and healthcare professionals have been produced. The brochures for patients and their families has been translated in 11 different languages. They are available on the E-IMD

website.

## Results and key findings

**Please discuss the results achieved in terms of outputs and (actual or expected) outcomes and their potential impact and use by the target group (including the socio-economic impact, the wider societal implications of the project and contribution to the policy development at all levels of governance (EU, MS, Regional and local).**

**1. Output**

E-IMD has become an important expert network, of 87 partners worldwide, for rare intoxication type metabolic diseases. The network meets annually to discuss project progress, research, patient management and best practice

**Potential impact and use by the target group**

This network provides high quality and accessible healthcare services to healthcare professionals, patients and family. The goal is to improve patients access to the best possible expertise, diagnosis and care available in the EU.

**2. Output**

The network has produced educational material and five live courses as well as one e-learning course for healthcare professionals working or training in the field.

**Potential impact and use by the target group**

The rarity of patients and the high phenotypic heterogeneity of RD combined with the lack of knowledge and training result in frequent delays in correct diagnosis and installation of appropriate care and treatment. This impacts survival and quality of life. E-IMD has been actively involved in improving the provision of training through the Orphan Europe Academy (now known as the Recordati Rare Diseases Academy Fondation d'entreprise, RRDA)

**3. Output**

E-IMD has expanded the network to Homocystinurias and methylation defects by applying to DG Sanco call 2012 (E-HOD): European network and registry for homocystinurias and methylation defects.

**Potential impact and use by the target group**

This project uses the same IT platform as E-IMD; therefore allowing economy of scale. In addition, the project "iNTD" which focuses on patients with neurotransmitter disorders and which has received seeding funding by a private sponsor (Dietmar Hopp Foundation) is also using the same IT and structure. Therefore, this project is innovative as it clusters 50 inherited metabolic diseases onto the same IT platform, sharing tools, comparing coherent data within and across pathologies and provides economy of scale and scope. Potentially E-IMD could cluster all inherited metabolic diseases (over 600 different known diseases).

**4. Output**

Patient registry for OAD and UCD following a cohort of 1009 patients in the EU.

**Potential impact and use by the target group**

Evidence has been produced to show that the existence of a rare disease registries impacts patient management by setting standards concerning tests to be performed, collection of clinical information etc.

The first E-IMD registry report shows variation in the diagnosis, management and access to

treatment in different countries/centres. The introduction of best practice guidelines should help to harmonise care. The longitudinal follow-up of this cohort will provide further information on adherence to the guidelines and differences in outcome, i.e. outcome of patients diagnosed though new-born screening compared to those diagnosed with onset of symptoms.

**5. Output**

E-IMD has shared experience with various other groups and networks, particularly in the reflection on European Reference Networks.

**Potential impact and use by the target group**

Three members of the advisory board serve on the EUCERD: Prof Ivo Baric (Croatia), Prof Matthias Baumgartner (Switzerland), and Samantha Parker (EBE member). Through this network, we are able to share learning with other European Reference Networks and registries. We have presented to the European Commission clustering meeting in October 2011 and have participated in and presented to the UCDC Annual Meeting on 13 July 2011 in Washington DC, EMA/EUCERD registry meeting on 4 October 2011 in London, the EAHC meeting on "European Actions to Improve the life of patients living with rare Diseases on 25-26 October 2011 in Luxembourg, the RE(ACT) meeting on 29 February 2012 in Basel, the CLIMB meeting on 26 May 2012 in Glasgow, the 1st Forum of Patients Association for Inherited Metabolic Diseases in Tokyo on 5 August 2012, the EPIRARE workshop on 8 October 2012 and 21-22 October 2013 in Rome, the IRDIRC meeting in Dublin on 16-17 April 2013, the European Conference on Rare Diseases and Orphan products (ECRD) meeting on 8-10 May 2014 in Berlin, and various meetings of national societies for Inherited metabolic diseases in partner countries. Furthermore, we have provided the scientific programme of the International Fulda Symposium 2012 ("Approaching the 'deep' metabolic compartment") on 17-19 October 2012 in Fulda, the Symposium for Hyperammonemia Research and Education (SHARE) meeting on 27-28 July 2013 in Amsterdam, the ICIEM satellite meeting on UCD ("Catalyzing new therapeutic approaches") on 1-2 September 2013 in Barcelona. E-IMD has welcomed new partners and collaborates with other UCD/OAD networks, creating an innovative multi-stakeholder registry model. We will continue to present at important national and international rare disease events after the end of the funding period.

## Coordination with other projects or activities at European, National and International level

### European level

On a European level E-IMD has been instrumental for the realization of the EU-funded activity "**European network and registry for homocystinuria and methylation defects, E-HOD**" (EAHC no. 2012 12 02; project coordinator: H. Blom, Freiburg) which aims to improve health for patients with homocystinurias and methylation defects. E-HOD uses the same IT as E-IMD for their registry thereby clustering diseases on the same platform. Both consortia have also organised joint meetings and will continue extending their collaboration. This increases efficiency, helps to reduce costs, reutilizes solutions per other purposes, and improves networking between experts, patients and industry. Disease clustering is continued by adding neurotransmitter disorders to the same platform (project title: **"International Working Group on Neurotransmitter Related Disorders, iNTD"**; project coordinator: T. Opladen, UKL-HD). New applications of the IT platform are under development. For example, an international expert group coordinated by UKL-HD has recently been invited to submit a full proposal for stage 2 of the evaluation within the Horizon 2020 call H2020-PHC-2014-two-stage. This new project (acronym: EVALNBS) focuses on the evaluation of newborn screening programmes in Europe.

E-IMD has also collaborated with **RD-Connect**. S. Kölker (UKL-HD) has been invited to

participate the Core Implementation Group (CIG). E-IMD has shared information and consent forms and has specified the list of common data elements (CDE) used for the E-IMD and E-HOD registry. An ID-Card (http://rd-connect.bibbox.org/home) for E-IMD has been created by G. Blandin (Marseille University) increasing the visibility of the E-IMD registry for patients and their families.

S. Parker (OE), I. Baric (UZMS), and M. Baumgartner (Zürich) are members of **European Committee Union Committee of Experts on Rare Diseases** (EUCERD) which aids the European Commission with the preparation and implementation of Community activities in the field of rare diseases. Among others they have worked on recommendations for patient registries for rare diseases ("EUCERD core recommendations on rare disease patient registration and data collection", 5 June 2013).

Clinical partners of the E-IMD consortium are members of the **Society for the Study of Inborn Errors of Metabolism** (SSIEM), the major scientific organization for inherited metabolic diseases in Europe. J. Zschocke (Innsbruck), C. Dionisi-Vici (Rome), U. Spiekerkoetter (Freiburg), I. Baric (UZMS), M. Dixon (GOSH), and J. Campistol (CIBER) are Council Members of the SSIEM. Annual consortium meetings have been organized as a pre-meeting to the Annual Symposium of the SSIEM in Geneva (2011), Birmingham (2012), Barcelona (2013), and 2014 (Innsbruck, planned). In 2013, an official satellite meeting was organised together with the UCDC consortium and NUCDF in Barcelona. This has helped to increase the visibility of the E-IMD activity and to report on major achievements and results. In addition, guideline group meetings have been synchronised with these meetings. For the 2015 symposium (Lyon), E-IMD members have been invited to organise a full session on European IMD networks within the main conference programme.

E-IMD has also collaborated with **ERNDIM**, the external quality assurance programme for amino acids, quantitative amino acids, and other metabolites detectable in body fluids. E-IMD partners from UKL-HD, GOSH, AMC, Prague, and Zürich organises numerous outcome laboratory tests for organic acids and acylcarnitines as proficiency tests. All metabolic labs involved in E-IMD participate the quality assurance programme on a regular basis.

To offer standardised and up-to-date training for trainees in Pediatric Metabolic Medicine, E-IMD has collaborated with the **Orphan Europe Academy** which has meanwhile become the **Recordati Rare Disease Academy Fondation d'entreprise (RRDA)**. The Academy was founded in 2000 and gained reputation for its high-quality, innovative scientific education. In October 2013 the Academy was granted foundation status under French law. Six training courses have been co-organised by RRDA and E-IMD. E-IMD partners [J. Walter (Manchester), S. Hannigan (CLIMB), S. Kölker (Heidelberg), R. Lachmann (London)] are members of the RRDA Board of Directors or the Scientific Committee, respectively. This collaboration is instrumental for capacity building and for providing education of enthusiastic colleagues in this field, with a particular focus of offering training for colleagues from countries with a poor infrastructure for IMD.

**The European Metabolic Disorders Alliance (EMDA)** has been founded in 2014 as a result of networking of PO groups involved in E-IMD. EMDA has been incorporated to support families, young peoples, adults and professionals throughout Europe who are affected by an IMD, with a particular focus on UCD, OAD and homocystinuria. To achieve this goal EMDA collaborates with E-IMD and E-HOD.

### International level

Starting with 28 European partners in 2011, E-IMD has managed to establish an international

network now including 87 partners from 25 countries on four continents.

To foster transatlantic collaboration on UCD, E-IMD has collaborated with the US American **Urea Cycle Disorders Consortium (UCDC)**. Both consortia have started harmonisation of their registries, have developed strategies for combined and comparative data analysis, and work together in developing guideline recommendations for UCD. E-IMD includes UCDC representatives, and vice versa, E-IMD is represented in UCDC. They have arranged various meetings and workshops, such as the 4th International Symposium on Urea Cycle Disorders ("Catalyzing new therapeutic approaches", Barcelona 1-2 September 2013) with more than 250 international participants. Similary, E-IMD has started collaboration with the **Japanese Urea Cycle Disorders Consortium (J-UCDC)** which has been founded in 2011.

**National level**

E-IMD partners are members of **national societies for IMD** in European and non-European countries. They have participated annual meetings of these societies and have reported about major achievements and results. This collaboration has fostered national guideline development and implementation of E-IMD recommendations in European and non-European countries.

E-IMD has also collaborated with **national PO groups**. Networking of PO groups within E-IMD was organised by CLIMB (UK). This includes the organisation of PO meetings, the item collection of the patient registry, guideline development and sending a survey to patients and their families on the needs of patients and families with rare UCD and OAD. Based on their interaction and on identifying the need for on overarching IMD Alliance in Europe, the European Metabolic Disorders Alliance (EMDA) has been founded.

**Strategic relevance, contribution to the Health Programme, EU added value and level of innovation.**

OAD and UCD are rare inherited metabolic diseases with a particularly low prevalence, and, consequently, relevant knowledge and expertise is rare. This singles them out as a distinctive domain of very high EU added-value. EU cooperation on the evaluation of inherited metabolic diseases with the E-IMD consortium will help to improve preventive medicine in European countries and will help to ensure that scarce knowledge has been shared and resources combined as efficiently as possible. Depending on the Member State and/or region where they live, EU citizens have unequal access to expert services and care options. Concerted action for the implementation and harmonisation of preventive medicine for inherited metabolic diseases will significantly help to reduce inequality, improve the diagnostic quality, reduce costs of national health services for life-long care of disabled individuals, and improve the quality of life of patients. Due to the enormous heterogeneity in Europe and the low incidence of inherited metabolic diseases, a transnational approach is indispensable to reach these goals and to exploit available data most effectively and efficiently.

Therefore, effective and efficient action for inherited metabolic diseases becomes connected to a coherent overall strategy for rare inherited metabolic diseases mobilising scarce and scattered resources in an integrated and well-recognised way, and integrated into a common EU effort. E-IMD is unique in that has developed a European patient registry and a specific information network between EU Member States which is the prerequisite to provide and disseminate accurate information in a format adapted to the needs of professionals and affected individuals, to promote optimised training to young scientists, and to develop

comparable epidemiological data at EU level. Since leading scientists of this proposal are key members of national and international societies for inherited metabolic diseases, the E-IMD consortium has enabled a rapid implementation of novel results and recommendations into daily practice. E-IMD has stimulated concerted action and has bundled existing national activities. It is complementary to and links to Orphanet and RD-Connect. E-IMD has also mapped onto the evolving national plans and strategies for rare diseases in that members of this group are members of their national networks. Registries are a precious resource of information in the area of rare diseases. The modular IT established for E-IMD has been reutilized and adapted to homocystinurias, methylation and folate metabolic disorders (within E-HOD) and neurotransmitter defects (within iNTD) thereby clustering more than 50 individual IMD by the use of the same IT. E-IMD will seek long-term sustainability through the national rare disease plans, Horizon 2020 and has made important steps towards a European Reference Network (according to EUCERD recommendations). We are aware of Europlan and PNMR2 (French Plan) in regards to the registers and European collaborations, and E-IMD is in line with these recommendations.

### Effectiveness of the dissemination

Dissemination is required to the different stakeholder groups to ensure engagement with the project to succeed in reaching its objectives. Dissemination is further required to ensure that patients are aware of the project and that healthcare professionals are properly trained. We have performed a stakeholder analysis before the start of the project to ensure that dissemination is tailored to the demands of individual stakeholders.

**Dissemination to patients:** Members of patient organisations have been asked to complete an online survey. The aim of the survey (available in four languages) was to understand how the quality of care and treatment of patients and their families received at their centre or hospital can better meet their needs and expectations. The role of E-IMD was to address any issues. The survey was anonymous.

**General dissemination:** has been performed via different sources: a) project website and web links for the general public, health care professionals, and patients/families; b) promotional E-IMD leaflet; c) Newsletters; d) annual (as well as final) user-friendly and easy-to-read electronic reports; e) information to existing IMD networks and societies.

**Presenting scientific findings and project results:** The scientific results has been disseminated through publications in peer-reviewed leading journals and presentations at well-established conferences and congresses. Three satellite meetings during the Annual SSIEM Annual Conference have been organised. This will be continued in 2014. In 2015, E-IMD will organize a full session on European IMD networks within the main programme of the SSIEM conference.

**Consensus care protocols:** Structured up-to-date information and consensus care protocols on OADs and UCDs have been made available for health care professionals, patients and other stakeholders. Quick reference guidelines for GA1, MMA/PA, IVA and UCD can be downloaded from the E-IMD website.

**Providing structured information material for patients and their families:** Information for patients and their families will be prepared as electronic (free download) brochures on the E-IMD website. Brochures have been written in English and have been translated into 10 other languages. Patient associations have consulted on the content and presentation of the brochures, have been involved in sub-working groups, translation and dissemination of information to patient groups. Logistic support for the preparation, translation and

dissemination of these brochures has been provided by OE.

**Patient group meetings:** Patient groups have worked alongside the leader of WP2 in brainstorming the aims and objectives of a European patient network meeting. Patient meetings have been organized alongside the annual E-IMD meeting during the SSIEM/ICIEM conferences. This early involvement of patients have allowed for more active involvement, afforded the opportunity to meet the researchers, understand the project aims and bring a patient perspective to the project. Patient groups have recognised the need for establishing a European umbrella organization for patients with inherited metabolic diseases. This has been realized by the foundation of the European Metabolic Disorders Alliance (EMDA; www.eumda.org).

**Providing structured training:** In cooperation with OEA which has become the RRDA we have organized six training course on inherited metabolic diseases for young trainees, in particular from countries with underdeveloped infrastructure for patients with these disorders. Originally, only one course was planned. However, since we have identified an enormous need for specialized training on OAD and UCD in Europe, E-IMD in collaboration with RRDA has decided to extend the number of provided courses. These course have been highly appreciated by participants.

**Advisory board meetings:** have been held annually to ensure transfer of knowledge and maintain enthusiasm for the project.

**Steering group meetings:** the steering group has met regularly to check progress against objectives and share information between members. Besides face-to-face meeting various telephone conferences have been organized and daily communication was done by e-mail.

**Monthly reports from the registry:** partners have received a monthly quality report on the number of patients in the registry for their centre including a detailed evaluation of the quality of entered data. This has helped to steadily increase the quality of the dataset. In addition, information on number of registered patients by partner and country have been provided via the public domain of the E-IMD registry in real-time mode.

### Conclusions and recommendations, sustainability of the project (after EC co-funding) and lessons learned.

E-IMD is highly successful in its objective of improving healthcare for patients with OAD and UCD and their families wherever they live in Europe. The network of participating centres of expertise is large and partners enthusiastically embrace the principles of widening access to and improving quality of diagnostic and clinical services. Information for patients, families and non-expert clinicians is available in a large variety of European languages. The establishment of the European registry is a major step forward in understanding some of the very complex clinical and biochemical issues related to OAD and UCD. The guidelines provide standards for improving the care of patients and decreasing variability. The network has engendered a momentum and enthusiasm among professionals working in this field to continue and build on what has been achieved so far – this is a good indicator that the network can be sustained through the understanding that collaboration is required in these rare diseases. However without European funding the network will work with reduced activity. This will inevitably imply that less developed countries or structures will be most disadvantaged when having to find national or local funding.

A recommendation from the network would be for centres of expertise to reduce the administrative burdens for members to participate in a network and registry by providing staff for the ethical approval, data entry and covering costs and time for experts to attend meetings.

All members of E-IMD feel very strongly that the network and registry must continue and that we should apply for European Reference Network status through the future call of interest. We include the sustainability subject on the agenda of all steering group meetings. We keep ourselves updated on new funding opportunities. We are aware of the cross border directive and its implications for ERNs and we will consider other sources of sustainability, including private funding, for parts of the network activities.

Within the Horizon 2020 call 2013, UKL-HD has coordinated an application for the project **"Evaluation of newborn screening and prevention programmes – EVALNBS"** and recently has been invited to submit a full proposal for Stage 2. This new project would provide an important new application for the IT and guidelines produced during the course of E-IMD. By this the achievements of E-IMD could be sustained and further extended by evaluating the impact of newborn screening in combination with evidence-based diagnostic and therapeutic algorithms on patients with rare IMD.

Continued clustering of disease groups of inherited metabolic diseases, vertical (target groups) and horizontal (geographical coverage) extension of the consortium and intensification of networking with other scientific consortia, patient support groups, stakeholders, healthcare professionals, national and EU health authorities shall be pursued. This network provides the field of metabolic diseases with tools, guidelines, training and knowledge to improve the care of patients with a, diagnosed or unclear diagnosed, inherited metabolic disease.

**SECTION VI**

**Horizontal Work packages**

**Work package title :** **Coordination of the project**
**Work package Number :** **1**
**Work package Leader :** **UKL-HD**
**Number of associated partners involved :** **12**
**Number of person/ days of this work package:** **462**
**Total budget of this work package:** **229 643 €**
**Starting Date. Ending date : :** **M1, M40**

**Project management**

**Management Plan** **yes**
**Sustainability plan available, describing the measures taken to ensure the continuation of the action after the end of the EC funding** **yes**
**Partnership Internal Agreement** **yes**

**Description of the work package:**

**Activities undertaken to ensure the coordination and management of the project and the partnership and to ensure that the activities are implemented as planned.**

**- Partnership management of tasks and achievements**
T(ask) 1.1: UKL-HD has carried out all the **overall management activities.** This has been done in close cooperation with those partners devoted to professional scientific, technological and administrative management of the E-IMD project. UKL-HD has successfully coordinated the network with strong leadership skills.
T1.2: **Internal partnership agreement** was drawn by UKL-HD, reviewed by the steering group and signed by all (associate and collaborating) partners. The partnership agreement clearly specifying major aims of E-IMD, agreed purposes and duration of the activity, definition and tasks of the decision-making bodies, accessibility to and use of the patient registry, and publication policy. Meeting summaries have been circulated to all partners and a précis posted on the website.
T1.3: **Communication** has been crucial to the success of E-IMD. UKL-HD has undertaken all possible measures to facilitate efficient communication processes and to comply with the previously agreed internal communication structure. A web-based project platform has been established including a document management system and communication functionalities that foster a continuous and transparent information flow between all partners. Various means of communication have been used such as face-to-face meetings, telephone and Skype conferences, e-mails and regular mail. To monitor progress and to solve problems WP leaders have reported to UKL-HD on a regular basis.
T1.4: UKL-HD has been in charge of all **financial issues**, whereas all partners have been solely responsible for providing consolidated costs statements and audit certificates to UKL-HD in due time. All annual consolidated costs statements and requests for annual prefinancing have been submitted in time to the Agency.
T1.5. **Coordinating scientific work**: UKL-HD has coordinated the general project activities of the whole consortium, whereas the WP leaders have coordinated their respective WP teams. Regular communication (scientific conferences, meetings, telephone conferences, e-mail conversation) between UKL-HD and the WP leaders as well as with all other partners have been performed. UKL-HD has successfully built links from the E-IMD with the US Urea Cycle Disorders

Consortium (UCDC, represented by Prof. Marshall Summar, Washington DC), with the SSIEM (Society for Study of Inborn Errors of Metabolism, various E-IMD partners are members of the SSIEM), the newly established Japanese UCD consortium (represented by Prof. Fumio Endo, Kumamoto), the dietitians' (represented by Reinhild Link, Wiesbaden) and the adult metabolic groups within the SSIEM (represented by Dr Robin Lachmann, London). The E-IMD network has grown from 1 coordinator, 12 associate and 15 collaborating partners in 15 countries to 87 partners in 25 countries (Australia, Austria, Belgium, Canada, Croatia, Czech Republic, Denmark, France, Germany, Greece, India, Italy, Japan, Netherlands, Poland, Portugal, Republic of Serbia, Romania, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, United States) on four continents (Europe, North America, Australia, and Asia).
T1.6. **Coordinating and managing the registry**: UKL-HD has been in charge of the coordination of the European registry, supervising the recruitment of study patients and reporting of follow-up data, and harmonising tools and protocols for the follow-up and management of patients. This has been performed within a team at UKL-HD including S. Kölker and P. Burgard as team supervisors and registry administrators, a data manager, a scientific collaborating partner coordinator, a biostatistics manager, and an IT manager. Milestones have been reached in time, all deliverables have been delivered.
T1.7. **Good clinical practices, ethical issues and protection of personal data**: have been secured by obtaining approval by institutional ERC, preparing SOPs for quality assurance and specific CRF to report written data of the E-IMD registry. Accessibility to the patient registry has been limited to those partners with written ethical approval. Support has been provided to all partners in obtaining their national or local ethical approval for the registry.

**- Management structure description, summary of the steering committee, advisory board**
The **advisory board** has been composed of all network partners. These members have the confidence of their national colleagues and have seen many or most of the OAD and UCD cases in their country. The advisory board is the principle decision-making body of E-IMD and has decided on the following: 1/ Mediate disputes between members, which cannot be settled by the members themselves; 2/ Validate requests to use the network data for further research or dissemination; 3/ Validate communication actions carried out in the name of the network. Decisions are taken by majority vote. In case of equality of votes, the project leader holds the casting vote. Decisions can be made in the absence of single advisory group members; the quorum for decising-making is 50% of advisory board members. The advisory board has met on a yearly basis, i.e. in Luxembourg (2011, kick-off), Geneva (2011, 1$^{st}$ annual meeting), Birmingham (2012, 2$^{nd}$ annual meeting), and Barcelona (2013, 3$^{rd}$ annual meeting). The annual meetings will be continued after the end of the funding period (Innsbruck 2014, 4$^{th}$ annual meeting). A summary of these meeting is available in the annex.
A **steering committee** composed of the lead of each work-package UKL-HD, CHRU-L, OE, BCHNHSFT, and additional support from the Zurich collaborating partners as well as PO groups (CLIMB, BOKS, VKS), has met quarterly to check progress against objectives. The following face-to-face meetings have been held and a summary is available in the annex: (1) Paris 23 May 2011, (2) Geneva 29 August 2011, (3) Zurich 17 November 2011, and (4) Paris 16 Jan 2012, (5) Paris 10 May 2012, (6) Birmingham 2 September 2012, (7) Paris 25 April 2013, (8) Paris 19 July 2013, and (9) Barcelona 1 September 2013. In addition, regular telephone conferences have been performed between these meetings.
In addition, WP-related working groups for evaluation (WP3), patient registry (WP4) and guideline development (WP5) have been established to optimize progress of the activity. Various PO group meetings have been organized. PO groups have actively contibuted in the network and representatives have participated the advisory board and have given advise to the steering group.

**- Description of the internal communication channels**
Communication has been crucial to the success of E-IMD. UKL-HD has undertaken all possible

measures to facilitate efficient communication processes and to comply with the previously agreed internal communication structure. A web-based project platform has been established including a document management system and communication functionalities that foster a continuous and transparent information flow between all partners. Various means of communication have been used such as face-to-face meetings, telephone and Skype conferences, e-mails and regular mail. To monitor progress and to solve problems WP leaders have reported to UKL-HD on a regular basis.

**- Problems that have occurred and how they were solved or envisaged solutions**

E-IMD has performed very well and has followed to proposed project plan mostly in time. All milestones have been reached and deliverables delivered.
The following problems occurred:
**1/ The employment of data managers** has been in time in the majority of partners but has been delayed in three partners (AMC, AZPD, GOSH) who have not managed to receive ethical approval and thus could not register patients and have not employed a data manager in 2011. In two other partners (CIBERER, HSJ), who have received ethics approval in time and have identified appropriate candidates for the position of the data manager, the employment of new staff has been moderately delayed due to time-consuming confirmation by the Ministry of Health, as a consequence of the financial crisis in Europe. In 2012, the employment of project-related staff has been completed; all above mentioned partners have overcome their initial problems and have caught up with E-IMD tasks. Finally, 1009 patients have been registered, i.e. 168% of the minmal project goal.
**2/ Ethical review process**: a source of significant variability in the activation process has been the ethical review process. The national and local regulations caused delay in some countries, whereas other partners did not even need to pass a formal ethical review process. There was also uncertainty in a few local ethical review boards whether a formal review process was required for a patient registry or not. Since this problem was caused by national discrepancies of specific regulations, the E-IMD consortium could not solve this problem on its own. It would be of great benefit for rare disease registries to harmonise regulations and to distinguish between non-interventional studies with low or even no risk of potential harm for participating individuals and other types of research, at a European level.
**3/ Project funding mechanism**: A major drawback was the funding mechanism of the activity. The activation process time and the number of patients registered were significantly different in associated and collaborating partners. Whereas associated partners received partial EU funding, collaborating partners collaborated on a voluntary basis but without financial compensation for their working time. Therefore, it can be assumed that the activation process would have been accelerated and the total number of patients would have been significantly increased, if a larger proportion of clinical partners had received project funding. In addition, the shared cost principle and the annual pre-financing procedure has been a challenge for the financial management of this project during the European financial crisis as hospital administrators have been unable to spend more than they received or to sign contracts of new employees without delay. In conclusion, the management of this project could have been improved if European regulations had been harmonious on a national level and the financial plan for such projects was more flexible.

**- Impact of possible deviations from the planned milestones and deliverables, if any**

Not applicable.

**- List of project meetings, dates, venues, annotated agenda, action-oriented minutes**

**Kick-off meeting:**
1-2 February 2011, Luxembourg

**Advisory board meetings** (including GDG meetings):

Advisory board meetings are performed annually and are synchronized to the annual symposia of the SSIEM (2011, 2012, 2014) and ICIEM (2013).

- 29-30 August 2011, Geneva
- 3-4 September 2012, Birmingham
- 1 September 2013, Barcelona
- 1 September 2014, Innsbruck (scheduled)
- 31 August 2015, Lyon (scheduled)

**Steering committee meetings:**
A steering committee composed of the lead of each work-package, and additional support from the Zurich collaborating partners as well as PO groups (CLIMB, BOKS, VKS), has met regularly to check progress against objectives. The following face-to-face meetings have been held:

- 23 May 2011, Paris
- 29 August 2011, Geneva
- 17 November 2011, Zurich
- 16 Jan 2012, Paris
- 10 May 2012, Paris
- 2 September 2012, Birmingham
- 25 April 2013, Paris
- 19 July 2013, Paris
- 1 September 2013, Barcelona

In addition, regular telephone conferences have been performed between these meetings.

**Agendas and minutes of advisory board and steering group meetings** are included in the annexes.

**Guideline development group (GDG) meetings**
Fourteen GDG meetings have been organized (UCD group: 3, MMA/PA group: 5, IVA group: 4, GA1 group: 2), eleven of them have been synchronised to above mentioned annual SSIEM and ICIEM symposia in order to reduce costs.

**PO group meetings**

- 13 Dec 2011, Paris
- 16 Jan 2012, Paris
- 26 May 2012, Glasgow
- 2-3 September 2012, Birmingham
- 12 July 2013, Crewe
- 3 September, Barcelona

**4th International Symposium on Urea Cycle Disorders "Catalyzing new therapeutic approaches"** (in collaboration with UCDC and NUCDF)
1-2 September 2013, Barcelona
This symposium was an official satellite meeting of the ICIEM 2013 symposium. More than 250 international experts have participated. This meeting is an important milestone in fostering transatlantic collaboration between UCDC and E-IMD consortia.
The prospectus of the satellite meeting is added in the annex.

**International FoNM 2012 symposium on "Approaching the 'deep' metabolic compartment** (in collaboration with Nutricia)
17-19 October 2012
This international symposium has gathered more than 150 participants from Europe and non-European countries, in particular the USA. E-IMD and UCDC consortium members have

presented latest news on intoxication type metabolic disorders and renowned international scientist have provided deep insights in basic research in neurometabolism. This interdisciplinary approach has aimed to foster translational medicine.
The programme of this symposium is added in the annex.

**- Amendments incurred or requested during the reporting period**
An amendment has been submitted and agreed on by the Agenda. The amendment included transfer of budget between partners CHRU L and OE, revised annex II and an extension of the project from 36 to 40 months (end date: 30th April 2014).

**- Changes in the partnership, if any**
The E-IMD consortium has increased from 28 partners in 2011 to 87 partners in 2014. Whereas the number of associated partners has remained unchanged, the number of collaborating partners has been more than quadruplicated.

**- Any changes to the legal status of any of the beneficiaries**
One partner (CIBERER), the Spanish network has changed its organisational form, name and acronym (CIBER) during the course of the project. This has been indicated to the EAHC project officer, and revised declaration of honour, legal entity, and letter of mandate have been provided by CIBER.

**- Financial management.**
UKL-HD has been in charge of all **financial issues**, whereas all partners have been solely responsible for providing consolidated costs statements and audit certificates to UKL-HD in due time. All annual consolidated costs statements and requests for annual prefinancing have been submitted in time to the Agency.

**- Conclusions**
E-IMD has been managed considerably well and has achieved all major project goals. The activity developed beyond expectations. However, management could have been facilitated and project achievements could have even been increased if the funding mechanism had been more flexible, the burden of bureaucracy had been lower and if national regulations underlying the ethical review process had been harmonised.

**List of deliverable(s) linked to this work package**

**Deliverable**

| # | Title |
|---|---|
| **3** | Interim report 1 |
| **4** | Interim report 2 |
| **7** | Annual meetings |
| **8** | Final report |

**Milestones reached by this WP**

| # | Milestone title | Month of achievement |
|---|---|---|
| **1** | Kick off meeting (Luxembourg, premises of the awarding authority) of the E-IMD consortium and the representatives of the EAHC/DG Sanco | 1 |
| **2** | Required staff is completed (i.e. no open positions) depending on the start of the project (M1-13) | 13 |
| **3** | Annual review written and compiled : M12, 24 | 24 |
| **4** | Final review written and compiled | 36 |

**Horizontal Work packages**

**Work package title :** **Dissemination of the project**
**Work package Number :** **2**
**Work package Leader:** **CHRU L**
**Number of associated partners involved :** **12**
**Number of person/ days of this work package:** **221**
**Total budget of this work package:** **114 573 €**
**Starting Date. Ending date : :** **M3, M40**

**Dissemination plan available** **yes**
**Project leaflet/brochure/newsletters submitted to EAHC** **yes**
**Project website: www.e-imd.org**
**The EU funding disclaim and EU logo are visible in the project website and public presentations** **yes**

**Description of the work package**

**- Description of the key messages.**

- Dissemination to patients: By use of an online survey we evaluated the quality of care and treatment of patients and their families in order to better understand their needs and expectations. As an important result of this survey the need for founding an umbrella organisation for rare inherited metabolic diseases has been identified. In 2013, the European Metabolic Disorders Alliance (EMDA) has been founded.
- General dissemination: We established a project website (www.e-imd.org) including helpful weblinks. To raise the awareness for E-IMD, a promotional leaflet has been circulated. By this and other means we have been able to triplicate the number of E-IMD members from Jan 2011 – Apr 2014. Electronic reports and newsletters have regularly informed about recent progress and major results of the project.
- Presenting scientific results: Seven peer-reviewed articles have been published, national guidelines have been made available via national guideline servers, six additional publication projects have been identified and draft manuscripts prepared. Three annual meetings have been organized and additional scientific meeting co-organised. Up-to-date information on the project have been presented on various international and national meetings as a poster or oral presentation.
- Consensus care protocols have been developed, quick reference guides for GA1, MMA/PA, IVA and UCD have been made available via the E-IMD website.
- Structured information materials for patients and their families have been developed and translated into 11 languages.
- Patient group meetings have been organized in parallel to annual E-IMD meetings.
- Structured training for trainees in Pediatric Metabolic Medicine have been provided via six international training courses in collaboration with OEA which has become RRDA.
- Regular annual and steering committees have been performed and minutes of these meetings have been circulated to inform all E-IMD members on most recent developments.

**- Visual project identity, including project logo, etc**

A project logo has been designed in M1 and, subsequently, has been used on the project website, the patient registry, brochures, presentations, posters and for other disseminations activities. The colour scheme of the website, patient registry, posters and presentations has included colours that match to the E-IMD project logo. This has increased the visual project

identity.


### Stakeholder analysis

| Stakeholder | Needs |
|---|---|
| Patients with OAD/UCD and their families | They are confronted with significant inequalities due to lack of existing knowledge, low evidence base of divergent treatment strategies, and limited availability of understandable information. Giving access to information and consensus expert advice helps empower patients allowing them to better understand their disease; this helps establish optimal medical support. Ultimately this is a step towards equity of information and care throughout the EU. A needs assessment will be carried out at the beginning of the project |
| Patient support groups | The process of interaction with national patient organizations will lead to improved dissemination of patient information. It may also lead to the establishment of novel patient groups in countries where none exist. E-IMD will work with Eurordis (see WP3) and involve patient groups in a project advisory role (several associations are aware of this project). |
| E-IMD associate partners | Keep informed about the project including administrative and financial questions.<br>Sharing expertise and networking. |
| E-IMD collaborating partners | Sharing expertise and networking. |
| Health care professionals (HCP): | Providing HCP with up-to-date information, consensus care protocols and standardised training will lead to improved medical quality and networking with experts and stakeholders. |
| Young doctors in training | Training and education |
| Scientific societies | Raise awareness.<br>Endorsement of best care practice guidelines |

| | |
|---|---|
| | developed in the group. |
| National and EU health authorities: Rare diseases and the gathering of expertise at a European level are an EU Priority. The EU recommends the setting up of national rare disease plans or strategies in all MS by 2013. E-IMD is completely complementary. Information about E-IMD progress will be given to EUCERD to assist with their decision making and policy priorities. | Sharing project results with coordinators of other similar rare disease networks. |

**Problem encountered**

Translation: Professional medical translations have been quite often of poor quality.

**How were problems resolved /limitations**

Translation: To increase the quality of medical translations E-IMD members from various countries have carefully revised all translations. This has slowed the process of translating brochures and has resulted in an increased workload of E-IMD partners for translations and back translations. Therefore, 11 instead of 16 translations as planned have been finalised so far.

**Conclusions and recommendations for the future**

Dissemination is required to the different stakeholder groups to ensure engagement with the project to succeed in reaching its objectives. Dissemination is further required to ensure that patients are aware of the project and that healthcare professionals are properly trained. Dissemination has been effective and has been adapted to the demands of individual stakeholders. All expectations has been met, all deliverables achieved in time. Translation of brochures has become time-consuming since professional translations were below the expected quality.

**Overview table showing the distribution and target for all project deliverables**

| # | Title | Distribution Channel | Target audience |
|---|---|---|---|
| **1** | E-IMD promotional leaflet (print and electronic version) | E-mail, mail, telephone | E-IMD consortium |
| **2** | Launch website and electronic newsletter | E-IMD website, e-mail, mail | All European metabolic centres and relevant stakeholders |
| **3** | Interim report 1 | E-IMD website | All European and international metabolic centres and relevant stakeholders |
| **4** | Interim report 2 | E-IMD website | All European and international metabolic centres and relevant stakeholders |
| **5** | Training course (Orphan Europe Academy) | E-IMD website, Orphan Europe Academy website, e-mail, mail | All European metabolic centres, in particular trainees from EU countries with underdeveloped services for OAD and UCD |
| **6** | European patient registry of OAD and UCD cases | E-IMD website (password-protected area for Consortium members) | Members of the E-IMD Consortium |
| **7** | Annual meetings | a) Confidential activity/financial report: E-IMD website (Password-protected area for Consortium members);<br>b) Public report: E-IMD website | a) Confidential activity/financial report: EC, Consortium members;<br>b) Public report: All European and international metabolic centres and relevant stakeholders |
| **8** | Final report | E-IMD website, mail | EC, all European metabolic centres and relevant stakeholders |
| **9** | Consensus care protocols and information brochures | E-IMD website | All European and international metabolic centres and relevant stakeholders |
| **10** | Evaluation of process and outcome indicators | E-IMD website | All European and international metabolic centres and relevant stakeholders |

**List of deliverable(s) linked to this work package**

**Deliverable**

| # | Title |
|---|---|
| **1** | E-IMD promotional leaflet (print and electronic version) |
| **2** | Launch website and electronic newsletter |
| **5** | Training course (Orphan Europe Academy) |

**Milestones reached by this WP**

| # | Milestone title | Month of achievement |
|---|---|---|
| **1** | Promotional leaflet completed and circulated | 3 |
| **2** | Web-based knowledge database established and in use (first version) | 18 |
| **3** | Participants of the training course registered | 24 |

**Horizontal Work packages**

**Work package title :** Evaluation of the project
**Work package Number :** 3
**Work package Leader:** OE
**Number of associated partners involved :** 2
**Number of person/ days of this work package:** 177
**Total budget of this work package:** 80 072 €
**Starting Date. Ending date : :** M1, M40

**Evaluation plan available:** yes
**External evaluation:** yes

**Description of the work package**

**- Description of process and outcome evaluation.**

**Process indicators:**
Agreed items to be included in the registry for data collection
Analysis of quality and completeness of records in the database
Agreed contents of website
Meetings held on schedule – SIGN methods applied

**Output/outcome indicators:**
Number of cases reported in the registry by country/centre
Analysis report on differences in diagnosis, treatment and outcome at start and end of project
Number of hits, unique visitors and enquiries to the website
Number of existing recommendations in Europe for OAD and UCD
Analysis of registry to show number of centres using E-IMD recommendations for OAD and UCD

**- Evaluation methodology: Evaluation questions, design, method, measurement instruments, task, responsibilities and timing.**
The evaluation report was led by S. Parker (Orphan Europe and EUCERD member), the members have included: S. Hannigan (CLIMB, UK), H. Meutgeert (VKS, Netherlands), M. Baumgartner (EUCERD, Switzerland), M. Summar (UCDC, USA), A. Rovsing (PND organisation, Denmark). The first meeting of the evaluation group was held on 13th December 2011 (see minutes in the annex) and the evaluation plan was agreed. The group used the following external and internal sources of data and information:

Sources of information:

1.1. Members of patient organisations were asked to complete an online survey. The aim of the survey, which was available in four languages, was to understand how the quality of care and treatment of patients and their families received at their centre or hospital can better meet their needs and expectations. The role of E-IMD was to address any issues. The survey was anonymous.

1.2. Patient organisations were asked to complete a short survey following the first patient meeting, held in Birmingham September 2012:

- What have been the most valuable learning points of this meeting for you?
- Following this meeting, what services would you like E-IMD to set up for the benefit of patients?

- What issues/topics would you like followed up at a future meeting?
- Do you have any further feedback?

1.3. Members of E-IMD were asked to complete a similar survey at the end of the project.

1.4. The website is analysed, on a monthly basis, for number of hits and unique visitors. We also follow up on the number of enquiries to the network coming from the website.

1.5. The patient registry has been externally reviewed by various expert agencies: data protection, ethical and scientific. The registry has been used to analyse the number of cases reported by country/centre, differences in diagnosis, treatment and compliance to the E-IMD recommendations for OAD and UCD.

**- Monitoring tools developed for data collection.**

The registry: number of patients, geographical coverage etc.
Monkey Survey questionnaires
Website
External review by expert agencies on data protection, ethical and scientific content of the registry

**- Problems encountered and suggestions for improvement**

The weaknesses of online surveys include low response rate (people don't feel engaged), time to translate documents and cultural differences in understanding. Semi-directed questionnaires could be useful but reduce the outreach and are more time consuming.
The registry is the ideal tool for monitoring management, adherence to guidelines and patient outcome. However 3-year project funding is insufficient to monitor longitudinal outcome data and to evaluate the impact of newly developed clinical consensus care guidelines on the health outcomes of affected individuals.

**Evaluation final report**

The evaluation report is available and a short summary for public dissemination will be placed on the E-IMD website.

**Conclusions and recommendations for the future**

The evaluation final report concludes that E-IMD is highly successful in its objective of improving healthcare for patients with OAD and UCD and their families wherever they live in Europe. The network of participating centres of expertise is large and partners enthusiastically embrace the principles of widening access to and improving quality of diagnostic and clinical services. Information for patients, families and non-expert clinicians is available in a large variety of European languages. The establishment of the European registry is a major step forward in understanding some of the very complex clinical and biochemical issues related to OAD and UCD. The guidelines provide standards for improving the care of patients and decreasing variability. The network has engendered a momentum and enthusiasm among professionals working in this field to continue and build on what has been achieved so far – this is a good indicator that the network can be sustained through the understanding that collaboration is required in these rare diseases. However, without European funding the network will work with reduced activity. This will inevitably imply that less developed countries or structures will be most disadvantaged when having to find national or local funding.

A recommendation from the network would be for centres of expertise to reduce the administrative burdens for members to participate in a network and registry by providing staff for the ethical approval, data entry and covering costs and time for experts to attend meetings.

| |
|---|
| All members of E-IMD feel very strongly that the network and registry must continue and that we should apply for European Reference Network status through the future call of interest. |

| **Objective 1** | | European patient registry to describe the natural history, epidemiology, and current diagnostic and therapeutic strategies for rare OADs and UCDs and to provide information to national and EU healthcare authorities | |
|---|---|---|---|
| **#** | **Process indicators** | **Output Indicators** | **Outcome indicators** |
| **1** | Agreed items to be included in the registry for data collection | Number of cases reported in the registry by country/centre | Analysis of report on differences in diagnosis, treatment and outcome at start and end of project |
| **2** | Analysis of quality and completeness of records in the database | | |
| **Objective 2** | | To provide European evidence-based consensus care protocols for OADs and UCDs | |
| **#** | **Process indicators** | **Output Indicators** | **Outcome indicators** |
| **1** | Agreed contents of the website | Number of hits, unique visitors and enquiries to the E-IMD website | Analysis of registry to show number of centres using E-IMD recommendations for OAD and UCD |
| **2** | Meetings held on schedule – SIGN methods applied | Consensus care protocols for OAD and UCD available on E-IMD website in main European languages.<br>Number of existing recommendations in Europe for OAD and UCD | |

**List of deliverable(s) linked to this work package**

**Deliverable**

| # | Title |
|---|---|
| **10** | Evaluation process and outcome indicators |

**Milestones reached by this WP**

| # | Milestone title | Month of achievement |
|---|---|---|
| **1** | Survey sent to stakeholders | 3 |

**Specific Work packages**

**Work package title :** **European patient registry**
**Work package Number :** **4**
**Work package Leader :** **UKL-HD**
**Number of associated partners involved :** **11**
**Number of person/ days of this work package:** **3102**
**Total budget of this work package:** **640 558 €**
**Starting Date. Ending date : :** **M1, M40**

**Description of the work package**

**Work progress and achievements:**

T(ask) 4.1 **Harmonisation of items**: A working group including associated partners and PO representatives have discuss and defined items to be collected in the registry. This has been achieved by M3. The dataset included a set of common data elements for all OAD and UCD and a set of parameters that have been tailored to the individual requirements of single OAD and UCD (e.g. key biomarkers).

T4.2 **European patient registry for OAD and UCD**: The web-based password-protected E-IMD patient registry has been programmed starting in M4. Subsequently, tests with virtual and real probands have been performed by the UKL-HD team (starting in M5) before the first version of the registry was launched in M7. The publicly accessible part of the E-IMD registry is available online at https://www.eimd-registry.org. Personalised access to the registry is limited to those who have been nominated as data managers and to centres who have received ethics approval Since then monthly updates of the registry have been performed enabling ongoing optimisation of the IT solution.

T4.3 **Natural history and outcome**: The registry includes data from 929 baseline visits, 1072 annual follow-up visits, 413 emergency visits and 14 fatal disease course visits of a total of 1009 patients (168% of the minimal project goal) with OAD (methylmalonic, propionic, isovaleric aciduria, glutaric aciduria type I) and UCD (inherited deficiency of N-acetylglutamate synthase, carbamylphosphate synthase 1, ornithine transcarbamylase, argininosuccinate synthase and lyase, and arginase 1). Data administration, statistical analyses and updating of results has been performed by UKL-HD. Case ascertainment of study patients has been provided by all partners and has been evaluated independently by the study team in UKL-HD based on inclusion and exclusion criteria as well as result of the diagnostic work-up.

Recruitment of patients and gathering of follow-up data has be performed by the listed partners on a European level. Countries with a decentralized care system for IMD required an increased data manager time compared to countries with centralised systems (e.g France, Spain). To describe the natural history and outcome all patients has been followed by a standardised comprehensive assessment schedule including basic patient data, family history, age at diagnosis, first symptoms, frequency and duration of hospitalisation, medical and developmental history, physical and neurological examination, MRI studies, neuropsychological tests, and quality of life assessment. On the average, registered patients have received 2.4 visits during the study period.

The minimal cumulative frequency of OAD and UCD patients in Europe was estimated to be 2.09 in 1 million citizens, but data showed significant variation between countries (range, 0.15 to 8.39).

T4.4 **Assessment of treatment efficacy and safety**: have been performed by standardised survey of treatment-related parameters, including daily intake of nutrients, anthropometrical

parameters, biochemical monitoring (general and specific metabolic follow-up parameters) as well as untoward events. Considerable variations in the diagnostic and therapeutic algorithm have been identified between countries and centres. The analysis has highlighted the need for harmonisation, and the result of the analysis have been used an important source for the development of evidence-based consensus care protocols for OAD and UCD (see WP5).

**If applicable, the reasons for deviations from Annex I and their impact on other tasks as well as on resource execution.**

Not applicable.

**A statement on the use of resources.**

There have been no major deviations to the planned person months in this work-package. The main cost in this work package is the employment of data managers in the participating centres, who were responsible for trying to capture data in their country. We have noted that the funding mechanism of 70% pre-financing and 30% after the final report has a negative impact on centres that have more financial pressure. These centres have not been able to spend the 100% planned budget but only up to a maximum of the pre-financing. Furthermore administrative structures and delays in achieving ethical approval meant that some centres employed full-time data managers for a shorter period rather than part-time over a longer period.

**Specific objective of this WP**

| | Title |
|---|---|
| **1** | European patient registry to describe the natural history, epidemiology, and current diagnostic and therapeutic strategies for rare OADs and UCDs and to provide information to national and EU healthcare authorities |

**List of deliverable(s) linked to this work package**

**Deliverable**

| # | Title |
|---|---|
| **6** | European patient registry of OAD and UCD cases |

**Milestones reached by this WP**

| # | Milestone title | Month of achievement |
|---|---|---|
| **1** | Web-based password-protected patient registry active ; start of data entry | 6 |
| **2** | Harmonisation of tools used for the follow-up of patients finished | 12 |
| **3** | Statistical analysis completed | 38 |

**Specific Work packages**

**Work package title :** **Consensus care protocols**
**Work package Number :** **5**
**Work package Leader :** **BCHNHSFT**
**Number of associated partners involved :** **11**
**Number of person/ days of this work package:** **286**
**Total budget of this work package:** **152 115 €**
**Starting Date. Ending date : :** **M7, M40**

**Description of the work package**

**Work progress and achievements:**

Consensus care protocols for OAD and UCD have been developed to evaluate the evidence base of common practice.

T(ask) 5.1 **Establishment of an international guideline developmental group (GDG):** The first step has been to establish international GDG and a lead for each group. Four GDG focusing on GA1 (lead: UKL-HD), UCD (lead: Zurich), MMA/PA (leads: Zurich, BCHNHSFT), and IVA (leads: Munich, Pittsburgh) have been composed of 12-25 experts. All GDG have been established and have started to work until M8. In each group there is a representative from a PO. There has been enthusiasm and willingness to participate from experts outside of the EU and E-IMD has welcomed this contribution. Therefore the guideline groups also collaborate and use resources from the USA, Australia, Canada, and Japan. This has fostered international collaboration and harmonisation of diagnostic and therapeutic algorithms on an international level. To save costs most GDG group meetings have been synchronized to the larger annual consortium meetings (M8, M21, M33). Additional meetings have been organized between annual consortium meetings.

T5.2 **Systematic literature review:** In addition to the evidence base provided by WP4 (European patient registry for OAD and UCD), a disease-specific and topic-related systematic literature review has been performed by all GDG. Relevant publications have been identified and evaluated using a standardized procedure in analogy to the methodology of SIGN (Scottish Intercollegiate Guideline Network; www.sign.ac.uk). Systematic literature review and evaluation of published literature has been completed until M21.

T5.3 **Evidence-based recommendations:** Based on T5.2 evidence-based recommendations have been formulated by GDG focusing on diagnostic procedures, therapeutic strategies, and follow-up monitoring. These recommendations have been discussed internely and subsequently have been revised by the GDG and external consultants. This process has been completed by all GDG until M21.

T5.4 **Consensus and dissemination:** Consensus has been reached by a consensus conference (M21) which has involved members of national and international societies for IMD. Within the following months consensus care protocols have been revised and submitted for publication. So far, the UCD and GA1 have been published in peer-reviewed journals, the MMA/PA recommendations have recently been accepted for publication, and the IVA recommendations are planned to be submitted in the second half of 2014. GA1 and UCD recommendations have been submitted to national authorities to receive national endorsement as a guideline. Condensed versions of all recommendations have been published on the website. To further investigate the use and usefulness of published GA1 and UCD guidelines, UKL-HD and Zurich have performed pilot studies showing that published guidelines have been widely used and accepted and that the use of guideline recommendations has had a positive impact on the health outcomes of affected individuals. This shows that a coordinated action of international experts can significantly influence diagnostic algorithms, treatment and care for patients with

rare diseases and can significantly improve the health outcomes of affected individuals within a relatively short time span.

T5.5 **Understandable and comprehensive information brochures:** Based on published recommendations understandable and comprehensive information brochures for patients and their families have been developed. Translation into 11 languages have been performed by BCHNHSFT, back translation by all partners. Brochures are available via the website as PDF documents.

T5.6 **Increasing awareness:** In countries with estimated high mortality of newborns with OAD and UCD, E-IMD partners have raised awareness amongst neonatologists and other relevant target groups by giving seminars on UCD and OAD, by networking with experts and families, and by providing update information on E-IMD activities. In addition, E-IMD has organised six training courses on IMD with a particular focus on UCD and OAD and on participants from countries with underdeveloped services for IMD.

**If applicable, the reasons for deviations from Annex I and their impact on other tasks as well as on resource execution.**
Not applicable.

**A statement on the use of resources, in particular highlighting and explaining deviations between actual and planned person months per work package and available resources.**
Not applicable.

**Specific objective of this WP**

| # | Title |
|---|---|
| **2** | To provide European evidence-based consensus care protocols for OADs and UCDs |

**List of deliverable(s) linked to this work package**
**Deliverable**

| # | Title |
|---|---|
| **9** | Consensus care protocols and information brochures |

**Milestones reached by this WP**

| | Milestone title | Month of achievement |
|---|---|---|
| **1** | First meeting of the guideline development group (GDG): identification of topics, establishment of working groups | 9 |
| **2** | Second meeting of the GDG: systematic literature search and evaluation completed, formulation of draft version of consensus care protocols finished | 21 |
| **3** | Third meeting of the GDG: revision of consensus care protocols finished | 33 |
| **4** | Translation of consensus care protocols into understandable information brochures for patients and their families is finished | 35 |

## SECTION VII

## ANNEXES

### WP 1

- **Management plan**
- **Sustainability plan**
- **Agenda and Minutes of E-IMD Steering committee meetings**
- **Programme of 4th International Symposium on Urea Cycle Disorders** on "Catalyzing new therapeutic approaches" (in collaboration with UCDC and NUCDF), 1-2 September 2013, Barcelona, Spain
- **Programme of International FoNM 2012 Symposium** on "Approaching the 'deep' metabolic compartment (in collaboration with Nutricia), 17-19 October 2012, Fulda, Germany

### WP 2

- **Dissemination plan**
- **Promotional leaflet** (see deliverable D1)
- **Brochures** for patients (at different age groups) and their families (English version)
- **Electronic newsletters 2011-2014** (see deliverable D2)
- **Posters** (Selection)
- **Presentations** (Selection)
- Press releases

### WP 3

- **Evaluation plan** (minutes of 13th December 2011 evaluation group meeting)
- **Evaluation report**

### WP 4 to WP 5

**The deliverables should be ordered following the deliverable table and presented as pdf files to be uploaded on the EAHC database**

**Deliverables:**

- D6 Patient registry of OAD and UCD cases
- D9 Consensus care protocols and information brochures

(To avoid redundancy we have added deliverables 6 and 9 only once according to the order of deliverables, but have not included them in the annexes in addition).

**Chronological publication list produced during the reporting period. Please include copies of the articles as pdf files.**

1. Kölker S et al. Diagnosis and management of glutaric aciduria type I – revised recommendations. J Inherit Metab Dis 2011; 34: 677-694.

2. Pena L et al. Natural history of propionic acidemia. Mol Genet Metab 2012; 105: 5-9.

3. Schreiber J et al. Neurologic considerations in propionic acidemia. Mol Genet Metab 2012; 105: 10-15.

4. Chapman KA et al. Acute management of propionic acidemia. Mol Genet Metab 2012; 105: 16-25.

5. Sutton VR, et al. Chronic management and health supervision of individuals with propionic acidemia. Mol Genet Metab 2012; 105: 26-33.

6. Häberle J, et al. Suggested guidelines for the diagnosis and management of urea cycle defects. Orphanet J Rare Dis 2012 ; 7 :32.

7. AWMF-Leitlinie Nr. 027-018 (Entwicklungsstufe S3): Glutarazidurie Typ I – Diagnostik, Therapie und Management. Published online at 31 March 2011. URL: http://www.awmf.org/leitlinien/detail/ll/027-018.html (German guideline for the diagnosis, therapy and management of patients with glutaric aciduria type I).

8. AWMF-Leitlinie Nr. 027-006 (Entwicklungsstufe S3) : Diagnostik und Therapie von Harnstoffzyklusstörungen. Published online at 09 July 2012. URL: http://www.awmf.org/leitlinien/detail/ll/027-006.html (German guideline for diagnosis and therapy for the diagnosis and therapy of patients with urea cycle disorders).

9. Baumgartner MR, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis, accepted for publication.

10. Kölker S, Dobbelaere D, Häberle J, Burgard P, Gleich F, Summar ML, Hannigan S, Parker S, Chakrapani A, Baumgartner MR, on behalf of the E-IMD consortium. Networking across borders for individuals with organic acidurias and urea cycle disorders: the E-IMD consortium. Manuscript in preparation.

11. Kölker S, et al. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 1. The initial presenation. Manuscript in preparation.

12. Kölker S, et al. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 2. The evolving clinical phenotype. Manuscript in preparation.