The E-IMD, E-HOD and iNTD family of registries

- Organic acidurias
- Urea cycle defects

Started in 2011 – ongoing
(Chafea no. 2010 12 01, Kindness for Kids and Dietmar Hopp Foundations)

Postauthorization registry for Ravicti™

- Homocystinurias
- Methylation defects
- Folate disorders

Started in 2013 – ongoing
(Chafea no. 2012 12 02)

Postauthorization registry for Cystadane™

- Neurotransmitter disorders
- BH_4 deficiencies
- Cerebral folate deficiencies

Started in 2014 - ongoing

All registries share the same basic IT platform

U-IMD and IMD registries

Existing IMD registries

EIMD
European registry and network for Intoxication type Metabolic Diseases

EHOD
European Network and Registry for Homocystinurias and Methylation Defects

iNTD
International Working Group on Neurotransmitter Related Disorders

IMDs without registries

Main objectives of U-IMD

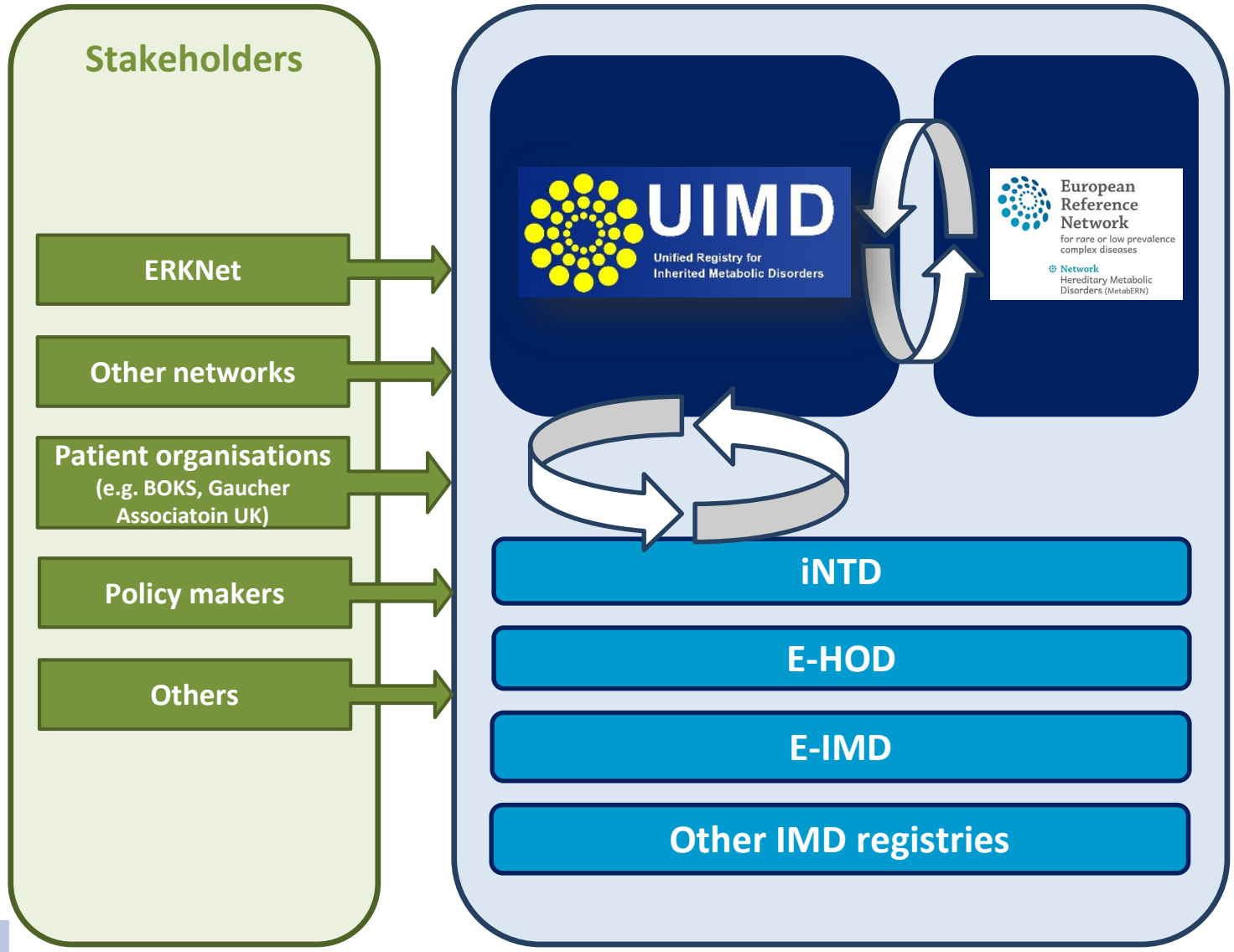
CHAFEA CALL for PROPOSALS - Support for New Registries HP-PJ-06-2016

Main objectives

- Creation of a **new IMD registry (U-IMD)** as official registry of **MetabERN**
- **Update of existing IMD registries** for the inclusion of the same data elements (starting with iNTD, later on E-IMD and E-HOD)
- Developing a standard for minimal core data sets shared by the MetabERN/U-IMD and the **European Rare Kidney Disease Reference Network** (ERKNet) registry.

UIMD
Unified Registry for Inherited Metabolic Disorders

Collaborative framework of U-IMD



User group of U-IMD

User Group

U-IMD will be available for all Members of MetabERN as well as for voluntarily collaborating health care providers (hospitals) outside of MetabERN. U-IMD is intended to be used by physicians treating patients with rare inherited metabolic disorders.

Access

U-IMD is a web-based patient registry. U-IMD will be accessible via the internet using password-protected user accounts and encrypted data transfer between server and client.

How to join U-IMD / How to submit patient data

- Contact the Coordinator (Prof. Stefan Kölker) with the expression of interest by email; your application will be evaluated by the U-IMD Steering Committee.
- Sign the U-IMD letter of agreement
- Using the template approved by IRB in University Hospital in Heidelberg, prepare and submit ethics application for U-IMD to your local IRB (respecting national/local standards).
- Receive personalized usernames and passwords ,and start data entry.

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Beneficiaries, work packages, and management

Beneficiaries and WPs

Stefan Kölker (UKL-HD)
WP 1 (Coordination)
Thomas Opladen (UKL-HD)
WP 4 (Patient Registry)

Viktor Kozich (VFN v Praze)
WP 2 Lead (Dissemination)

Carlo Dionisi Vici (OPBG)
WP 3 (Evaluation)
E-IMD Network Representative

Angels Garcia Cazorla (HSJD)
iNTD Network Representative

Maurizio Scarpa (HSK-WI)
MetabERN Coordinator

Project Management

Steering Group

- Work Package Leaders, one official representative from E-IMD, E-HOD and iNTD, MetabERN and PAGs
- WP 1 lead is U-IMD coordinator
- Coordinates and monitors implementation of the project
- Reports to Members Board

Members Board

- All MetabERN Members signing the Internal Partnership Agreement
- Primary decision-making and arbitration body
- Is informed by the Steering Group on the proceedings of the project during annual meetings
- Retains right to decide on usage of data

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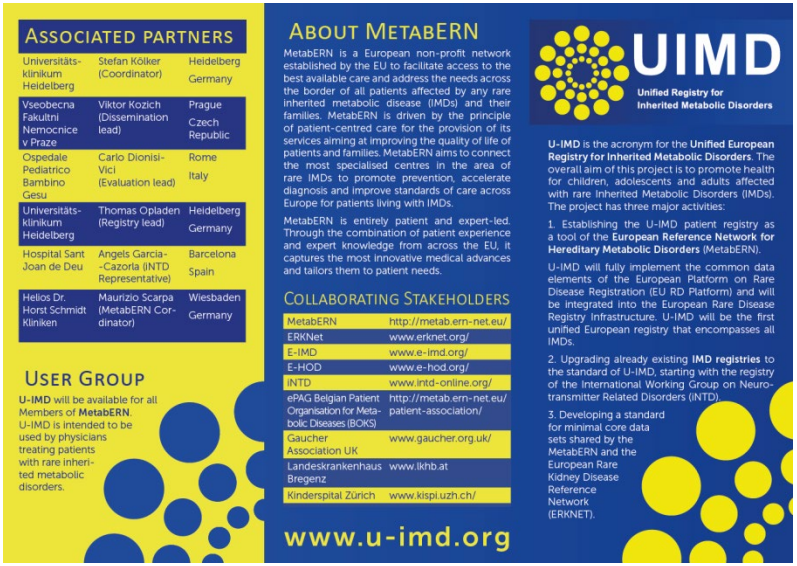
Timeline, milestones and deliverables

Number	Deliverable (D)/ Milestone (M)	WP	Due Month
D2.1 (MD.3)	Leaflet	WP2	3
D2.3 (MD.5)	Web-site	WP2	3
MS1	Kick-off meeting	WP1	3
MS2	Internal partnership agreement	WP1	3
MS3	Workshop on the data model of U-IMD	WP4	6
D4.4	User manual for data entry	WP4	9
D4.1	Patient registry	WP4	12
MS4	Staff recruitment completed	WP1	12
MS5	Presentations to stakeholders year 1	WP2	12
D4.5	Report on the development of a minimal core data sets	WP4	12
MS11	Patient registry established	WP4	12
M6	Annual meeting of evaluation group 1	WP3	15
D1.1	Minutes of annual meeting 1	WP1	15
D4.2	Interoperability of U-IMD and iNTD	WP4	18
MS12	Interoperability between U-IMD and iNTD	WP4	18
D1.4 (MD.1)	Interim report	WP1	18
D3.2	Report on the evaluation plan	WP3	24
MS7	Presentations to stakeholders year 2	WP2	24
D1.2	Minutes of annual meeting 2	WP1	27
MS8	Annual meeting of evaluation group 2	WP3	27
D4.3	Report on the analysis of data collected in the registry	WP4	33
D3.3	Report on the evaluation of data collected in the registry	WP3	33
D3.4	Report on the evaluation of mode of data collection	WP3	33
D1.3	Minutes of annual meeting 3	WP1	36
D3.1	Evaluation report	WP3	36
D1.5 (MD.2)	Final report	WP1	36
D2.2 (MD.4)	Layman version of the final report	WP2	36
M9	Presentations to stakeholders year 3	WP2	36
M10	Annual meeting of evaluation group 3	WP3	36

WP2 – Dissemination

Logo



Associated Partners

Universitäts-klinikum Heidelberg	Stefan Kölker (Coordinator)	Heidelberg Germany
Vseobecna Fakultni Nemocnice v Praze	Viktor Kozich (Dissemination lead)	Prague Czech Republic
Ospedale Pediatrico Bambino Gesu	Carlo Dionisi-Vici (Evaluation lead)	Rome Italy
Universitäts-klinikum Heidelberg	Thomas Opladen (Registry lead)	Heidelberg Germany
Hospital Sant Joan de Deu	Angels Garcia--Cazorla (iNTD Representative)	Barcelona Spain
Helios Dr. Horst Schmidt Kliniken	Maurizio Scarpa (MetabERN Coordinator)	Wiesbaden Germany

User Group

U-IMD will be available for all Members of **MetabERN**. U-IMD is intended to be used by physicians treating patients with rare inherited metabolic disorders.

About MetabERN

MetabERN is a European non-profit network established by the EU to facilitate access to the best available care and address the needs across the border of all patients affected by any rare inherited metabolic disease (IMDs) and their families. MetabERN is driven by the principle of patient-centred care for the provision of its services aiming at improving the quality of life of patients and families. MetabERN aims to connect the most specialised centres in the area of rare IMDs to promote prevention, accelerate diagnosis and improve standards of care across Europe for patients living with IMDs.

MetabERN is entirely patient and expert-led. Through the combination of patient experience and expert knowledge from across the EU, it captures the most innovative medical advances and tailors them to patient needs.

Collaborating Stakeholders

MetabERN	http://metab.ern-net.eu/
ERKNet	www.erknet.org/
E-IMD	www.e-imd.org/
E-HOD	www.e-hod.org/
iNTD	www.intd-online.org/
ePAG Belgian Patient Organisation for Metabolic Diseases (BOKS)	http://metab.ern-net.eu/patient-association/
Gaucher Association UK	www.gaucher.org.uk/
Landeskrankenhaus Bregenz	www.lkhb.at
Kinderspital Zürich	www.kispi.uzh.ch/

www.u-imd.org

UIMD
Unified Registry for Inherited Metabolic Disorders

U-IMD is the acronym for the **Unified European Registry for Inherited Metabolic Disorders**. The overall aim of this project is to promote health for children, adolescents and adults affected with rare Inherited Metabolic Disorders (IMDs). The project has three major activities:

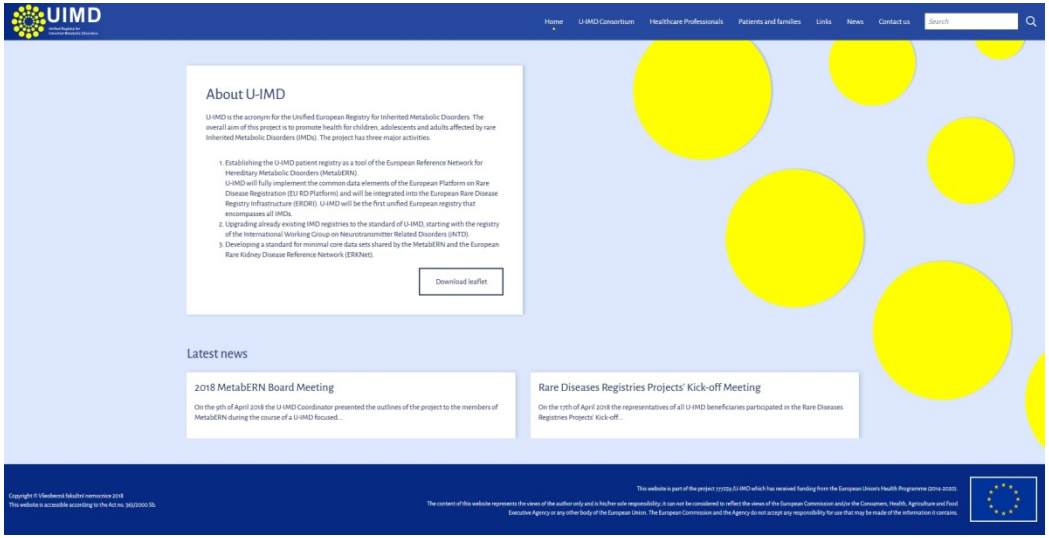
1. Establishing the U-IMD patient registry as a tool of the **European Reference Network for Hereditary Metabolic Disorders** (MetabERN).

U-IMD will fully implement the common data elements of the European Platform on Rare Disease Registration (EU RD Platform) and will be integrated into the European Rare Disease Registry Infrastructure. U-IMD will be the first unified European registry that encompasses all IMDs.

2. Upgrading already existing **IMD registries** to the standard of U-IMD, starting with the registry of the International Working Group on Neurotransmitter Related Disorders (iNTD).

3. Developing a standard for minimal core data sets shared by the MetabERN and the European Rare Kidney Disease Reference Network (ERKNET).

Leaflet



Website: http://u-imd.org/

UIMD
Unified Registry for Inherited Metabolic Disorders

WP4 – Concept of the U-IMD registry

The endeavor of building a unified IMD registry carries in itself **certain limitations** related to the diverse nature of the **heterogeneous etiological and clinical spectrum of IMDs** to be covered.

Solution

- Limitation of data collection to a minimal set of **common data elements (CDEs)**
- Use of **controlled dictionaries** for the description of the clinical phenotype and medication, as well as **standardized tools** for assessment of development, quality of life, and patient perspective.

This allows to compare key parameters intra- and inter-individually as well as across different diseases and disease groups, and guarantees interoperability with other registries committed to the same standards.

WP4 – Modular design of the U-IMD registry

Module 1
Common data elements

- **Common Data Elements (CDE)** developed by The European Commission's Joint Research Centre (DG JRC) for the EU RD Platform

Module 2
Phenotype

- **Human Phenotype Ontology (HPO)** as an established, controlled and standardized vocabulary for phenotyping clinical abnormalities
- **Results of standard IQ tests**

Module 3
Patient perspective

- Pediatric Quality of Life Inventory (**PedsQL**) and World Health Organization Quality of Life (**WHOQOL**), both questionnaires can be self-administered by patients**,** and are translated and validated in multiple languages. The WHO Disability Assessment Schedule 2.0 (**WHODAS 2.0**) will be augmented by a pediatric disability score.

Module 4
Drug treatment

- Drug treatment will be coded using the WHO Anatomical Therapeutic Chemical (**ATC**) classification system as standardized vocabulary. ATC was developed by the WHO to serve as a tool for drug utilization research.

Module 5
Metabolites

- A selection of disease specific metabolites and standard laboratory parameters will be offered, equialent to the respective selection of the Inborn Errors of Metabolism Knowledgebase (**IEM Base**).

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WP4 – Modular design of the U-IMD registry

Module 1
Common data elements

- **Common Data Elements (CDE)** developed by The European Commission's Joint Research Centre (DG JRC) for the EU RD Platform

SET OF COMMON DATA ELEMENTS FOR RARE DISEASES REGISTRATION

GROUP	ELEMENT N°	ELEMENT NAME	ELEMENT DESCRIPTION	CODING	COMMENT
1. Pseudonym	1.1.	Pseudonym	Patient's pseudonym	• String	The JRC is working on providing a
2. Personal information	2.1.	Date of birth	P		
	2.2.	Sex	P		
3. Patient Status	3.1.	Patient's status	P		
	3.2.	Date of death	P		
4. Care pathway	4.1.	First contact with specialised centre	D s		
5. Disease history	5.1.	Age at onset	Age at which symptoms/signs first appeared	• Antenatal • At birth • Date (dd/mm/yyyy) • Undetermined	
	5.2.	Age at diagnosis	Age at which diagnosis was made	• Antenatal • At birth • Date (dd/mm/yyyy) • Undetermined	
6 Diagnosis	6.1.	Diagnosis of the rare disease	Diagnosis retained by the specialised centre	Orpha code (strongly recommended – see link) / Alpha code/ ICD-9 code/ ICD-9-CM code / ICD-10 code	http://www.orphadata.org/cgi-bin/inc/product1.inc.php
	6.2.	Genetic diagnosis	Genetic diagnosis retained by the specialised centre	International classification of mutations (HGVS) (strongly recommended – see link) / HGNC / OMIM code	http://www.hgvs.org
	6.3	Undiagnosed case	How the undiagnosed case is defined	• Phenotype (HPO) • Genotype (HGVS)	
7. Research	7.1.	Agreement to be contacted for research purposes	Patient's permission exists for being contacted for research purposes	• YES • NO	
	7.2.	Consent to the reuse of data	Patient's consent exists for his/her data to be reused for other research purposes	• YES • NO	
	7.3.	Biological sample	Patient's biological sample available for research	• YES • NO	If YES answer question 7.4
	7.4.	Link to a biobank	Biological sample stored in a biobank	• YES (if appropriate use link) • NO	https://directory.bbmri-eric.eu
8.Disability	8.1.	Classification of functioning/disability	Patient's disability profile according to International Classification of Functioning and Disability (ICF)	• Disability profile / Score	http://www.who.int/classifications/icf/whodasii/en/

http://www.erare.eu/sites/default/files/SetCommonData-EU%20RD%20Platform_CDS%20_final.pdf

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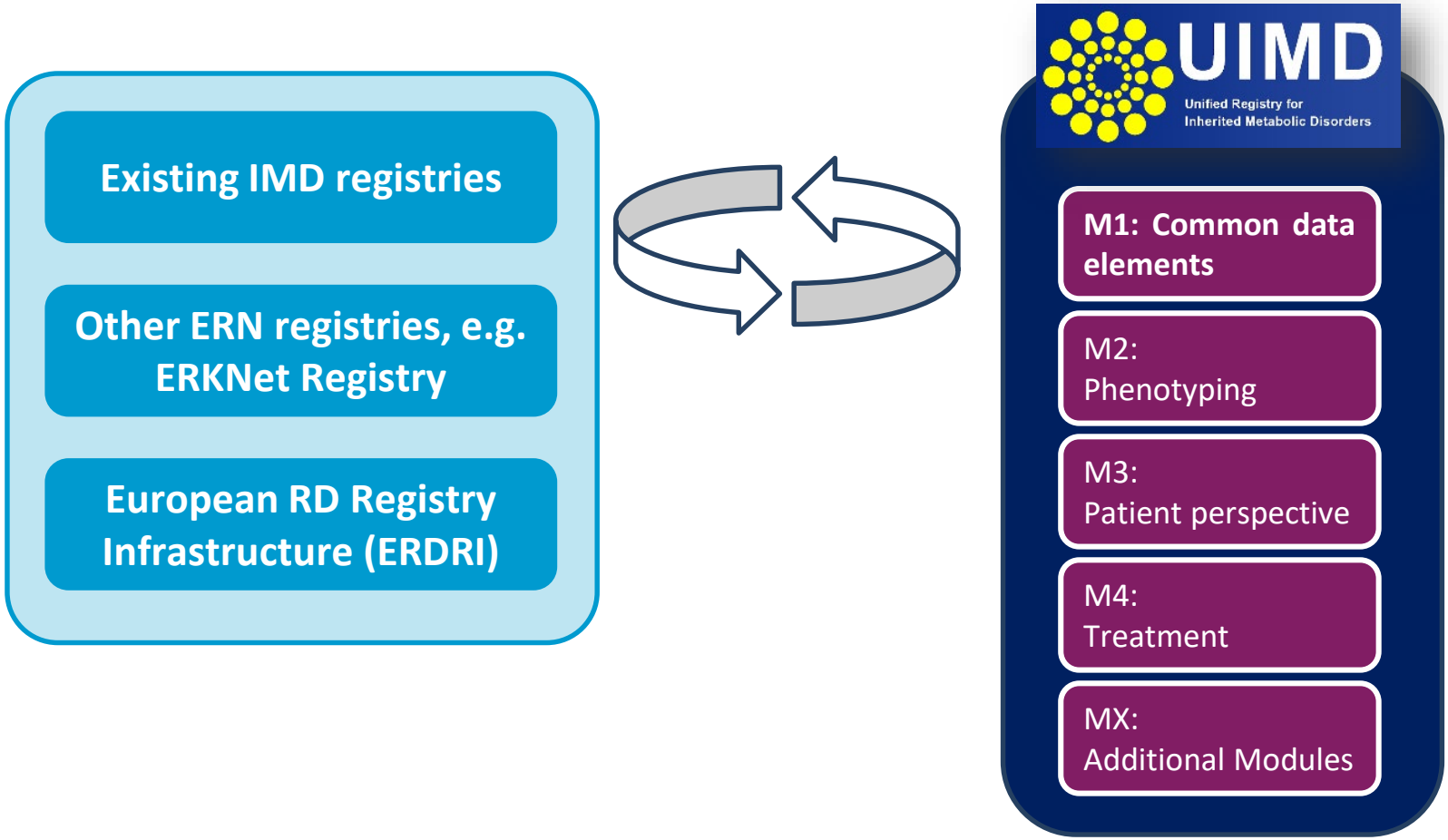
WP4 – Module 1 as a universal connecting element



UIMD
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U-IMD Registry scheduled to go online until February 2019

Advantages and Limitations of available Nosologies for IMDs

WP4 – Nosology used by the U-IMD registry

Among the various coding systems used by the U-IMD registry the nosology for disease coding is of greatest importance. The U-IMD Beneficiaries intensely discussed various available options with special consideration of:

- **Project timeline**
- **Need for stable and reliable case definition**
- **Prospects of forming future collaborations**

Several of the obvious candidates for the future U-IMD nosology had to be dismissed, for various reasons like:

- **ICD10 for lack of granularity**
- **Orphanet Codes due to often blurring the line between a strict nosology and a phenotype and severity focused differentiation system (Orphanet Codes will still be used as a tool for further characterization but not for primary case definition)**
- **SSIEM codes due to being in need of a revision for quite a while**

U-IMD finally decided on employing the proposed nosology of inborn errors of metabolism developed among others by Carlos Ferreira et al. (Genet Med 2018, DOI: 10.1038/s41436-018-0022-8). Among the leading arguments for this decision were:

- **High level of actuality and availability**
- **Satisfies the need for clear case definitions**
- **Existing linkages to MIM Codes, Orphanet Codes and HMDB Codes**
- **Prospect of cooperation between U-IMD and the IEM Database.**

WP4 – Defining a case in U-IMD

A. DISORDERS OF NITROGEN-CONTAINING COMPOUNDS

1. Disorders of pyrimidine metabolism
2. Disorders of purine metabolism
3. Disorders of nucleotide metabolism
4. Disorders of creatine metabolism
5. Disorders of choline metabolism
6. Disorders of glutathione metabolism
7. Disorders of ammonia detoxification

N-acetylglutamate synthase deficiency
Carbamoylphosphate synthetase I deficiency
Ornithine transcarbamylase deficiency
Argininosuccinate synthetase deficiency

Additional Information saved after selecting disease

Alternative IEM Name	Mode of Inheritance	Gene Name	MIM Number	IEM CODE	ORPHA Number	ORPHA Disease Name
Citrullinemia	AR	ASS1	603470	IEM0059	247525	Citrullinemia type I

Case definition also possible by choosing **IEM Code** or **Gene Name** (+ additional specification if ambiguous)

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