



Programme of community action in the field of health (2008-2013)

**European registry and network for
Intoxication type Metabolic Diseases (E-IMD)
Contract no: 2010 12 01**

Deliverable 6: European patient registry of
OAD and UCD cases
June 2014

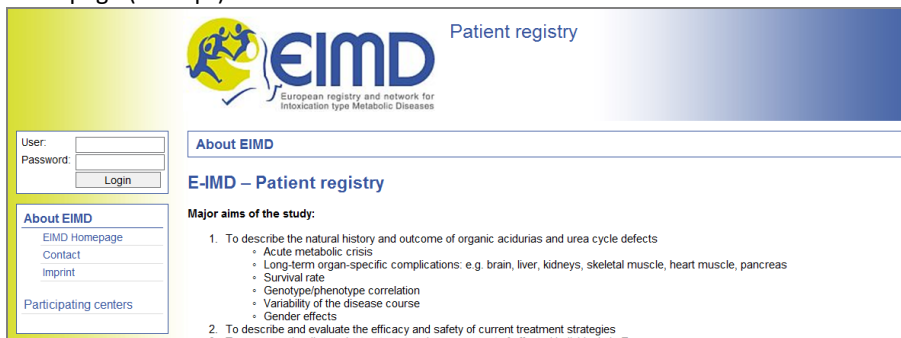
User manual

Patient registry

1. First steps

The web-based E-IMD patient registry is located at <https://www.eimd-registry.org>. By entering this link to your browser, the front page “About EIMD” appears on your screen. This page is open to public.

Front page (excerpt)



The front page contains

- general information about E-IMD
- a link to the E-IMD website (www.e-imd.org)
- a contact form
- imprint
- information on **participating centres** (address, phone, fax, e-mail, contact person, and number of total and active study patients)

If you click on “**Participating centres**” a list of **clinical E-IMD partners** appears on the screen. This list is sorted alphabetically using the ISO standard country code (e.g. CH for Switzerland, AT for Austria, DE for Germany...). All study centres in each country are listed. Up-to-date information on registered patients is provided for each centre. If you click on a centre you can get more information (address, phone, fax, e-mail, website, study investigators). If you click on the name of a **study investigator**, you can contact him/her directly by e-mail. New study investigators can be added by the administrator.

Note:

Please read through the information of your centre carefully and return **any requests for changes** to the administrators of the patient registry by e-mail (Stefan.Koelker@med.uni-heidelberg.de or Peter.Burgard@med.uni-heidelberg.de).

List of contact addresses of clinical E-IMD partners and study investigators

Germany	
Düsseldorf Universitätsklinikum Düsseldorf, Zentrum für Kinder- und Jugendmedizin	Registered patients - Total: 0 - Active: 0
Freiburg Universitätsklinikum Freiburg, Zentrum für Kinder- und Jugendmedizin	Registered patients - Total: 0 - Active: 0
Hamburg Universitätsklinikum Eppendorf, Klinik für Kinder- und Jugendmedizin	Registered patients - Total: 0 - Active: 0
Heidelberg Universitätsklinikum Heidelberg, Zentrum für Kinder- und Jugendmedizin	Registered patients - Total: 38 - Active: 38
Address: Im Neuenheimer Feld 430 D-69120 Heidelberg Phone: +49 622 156 4002 Fax: +49 622 156 5565 Email: Stefan.Koelker@med.uni-heidelberg.de www: www.klinikum.uni-heidelberg.de/kinder	Study investigators: Stefan Kölker Peter Burgard Kathrin Zangerl Friederike Hörster Christian Staufner Nikolas Boy Jana Heringer
Munich Klinikum der Universität München, Dr. von Haunersches Kinderspital	Registered patients - Total: 0 - Active: 0

How to activate your profile

The front page also contains two input boxes for entering your **user name** and **password**. To activate your profile you first need to send the **written ethics approval** of your local IRB or EC. Furthermore, provide us with the name of your local **data manager** and **other colleagues** who will enter patient data (if applicable). Please send a scanned file of this document to the registry administrators by e-mail (Stefan.Koelker@med.uni-heidelberg.de or Peter.Burgard@med.uni-heidelberg.de).

Subsequently you will receive your:

- **User name** (this cannot be changed by you; if you want to change it, please inform the administrator)
- **Password** (must be changed by you after the first login)

Note:

After the **first login** to the password-protected area, you are asked to **change your password**.

The **new password** must contain **8-15 characters** and at least **2 variations** (capital letters, digits). If the new password does not meet these formal requirements, you will not be able to save it.

Example (for a correct password):

Murakami1Q84

Example (for an incorrect password):

winniepooh

Please note that the new password is only known to you. **Keep it in a safe place!**

How to change your password

You are asked to generate a new password **at least every 180 days** (the time left before changing the new password is shown after each successful login). To change the password, please click on **“User settings”** which you find on the left menu. Please enter the new password, repeat and save it.

When login fails or you have forgotten your password

If you have **forgotten your password** or if you have **entered a wrong password five times**, your account will be blocked and you will not be able to get access to the registry.

Note:

If your account is blocked, please inform the patient registry administrators by e-mail (Stefan.Koelker@med.uni-heidelberg.de or Peter.Burgard@med.uni-heidelberg.de). They are able to unblock your account and to provide you with a new password (which you need to change again after first login, see above).

2. How to use the patient registry

Boxes

Throughout the registry, you will find different types of boxes:

- **Tick boxes** (to choose one or more options)
- **Pull down menus** (to choose an option from a predefined list)
- **Input boxes** (to fill in digits and/or characters)
- **Free text boxes** (to add important information). Please use these text boxes carefully and only if necessary. The length of information is restricted to **150 characters**.

Add a new patient

Please click on **“Patient registry”** which you find in the left menu.

How to add a new patient to the registry:

For most patients, you will choose the option **“Regular study patient”**. This means that the patient is alive while registering and, subsequently, is followed on a regular basis by you or your colleagues. If you want to enter data of a deceased patient whose diagnosis has been made after his/her death and who has not been enrolled to the study before, please choose the option **“Fatal disease course”**.

For all study patients, you need a written informed consent before starting data entry! All colleagues who enter patient data have to take care that written informed consent has been given. They are also responsible for the availability of properly filled and duly signed informed consent forms. Please keep the signed informed consents in a safe place. For patients with a fatal disease course, please note that patients who died before the start of E-IMD (i.e., January 1, 2011) are not eligible for this project.

When adding a new patient, first check eligibility!

A new patient can only be enrolled if the following criteria are fulfilled:

- **Confirmed** or at least **highly likely** diagnosis of an **OAD** (PA, MMA, IVA, or GA-I) or **UCD** (NAGS, CPS1, OTC, ASS, ASL, ARG1 or ORNT1 deficiency)
- **Signed informed consent** is available
- **No exclusion criteria** are known
 - No metabolic derangement caused by other metabolic diseases (e.g. fatty acid oxidation defects, mitochondrial disorders)
 - No unrelated serious comorbidities (e.g. Down syndrome, Kernicterus)

If one or more of these criteria are not fulfilled, you will receive the message **“Registry for this patient not eligible.”** In other words, enrolment of this patient is impossible.

Patient basic data

If all criteria are fulfilled, you will move forward to the **patient basic data** form.

Note:

It is very important that you fill in this form correctly. **After saving this form you will only be allowed to correct the items “gender”, “date of birth” and “ethnic background” before you start with the baseline visit!** Therefore, before you press “Save” **please check twice** that these data are correct.

When the data are correctly entered, a unique **patient identity number (patient-ID)** will be generated after saving this form (e.g. 001-003) and the status of the form changes to **“Completed”**. The patient will be added to your centre’s list of patients.

Note:

To reliably identify each of your study patients, please generate a **key list** (if this is allowed in your country) including the name and the identity number of study patients followed by your centre. Only you will know which patient-ID belongs to which patient. For the sake of data protection, the patient registry does not contain this information. Furthermore, the central study office (University Hospital Heidelberg) does not receive this information. In other words, **only you will be able to identify a specific patient followed by your centre!** Please keep the patient-ID list in a safe place!

Example: Correctly filled patient basic data form (before pressing the “Save” button)

Patient basic data

Center: Heidelberg, Universitätsklinikum Heidelberg, Zentrum für Kinder- und Jugendmedizin » Patient: New patient
Form status: -EMPTY-

Patient-ID Will be generated after saving...
Patient type Regular study patient

Date of written informed consent (DD/MM/YYYY)

Gender

Date of birth (MM/YYYY)

Ethnic background

Note: After saving of baseline visit, further changes of gender, DOB and ethnic background are not possible.

Country

Countries in which parents have been born:
Mother
Father

Number of other family members with the same disease:

[« Back to patient registry](#)

[» Top of page](#)

**Additional explanations
for the form “patient
basic data”**

- **Date of written informed consent:** A baseline visit cannot be performed before the day that the written informed consent is received. In the above mentioned example, April 1, 2011 would be the first possible date for the baseline visit, whereas March 31, 2011 would not be accepted.
- **Date of birth:** Please note that for data protection you can only enter the month and year of birth but not the complete date of birth.

- **Ethnic background:** This information is required for the 4-variable **MDRD** (=modification of diet in renal disease) **formula** which is used for the estimation of the glomerular filtration rate using serum creatinine in adults (Levey et al. Clin Chem 53: 766-772, 2007). If you should face any ethics problems with this item, please leave this information open.
- **Number of known family members with the same disease:** If you choose “2” (or another number) instead of “none”, a new field opens. This new field allows you to specify the degree of relationship between the other family members and the study patient (using a pull down menu) and to specify whether these family members are also E-IMD study patients.

If you click on “**Back to the patient registry**” you will return to your centres list of patients.

Baseline visit

To start entering the baseline visit, please click on a patient. A new field opens. On the right side you find a box with the headline “**Add a visit for this patient**”. Before the baseline visit is completed, you only have the option to choose “**Baseline visit**”. Please press “**Add...**”.

A new window opens. Please enter a **correct visit date** (i.e. not before the date of written informed consent has been given). At the top of this window you find a **list of forms** to use for the baseline visit. By clicking on this list, you can select a form and enter the required data. After entering data the status changes from “**EMPTY**” to “**Incomplete**” (if at least one relevant box has been left empty) or “**Completed**” (if relevant information is filled in completely and correctly).

List and status of forms

Select form...	Status
» Baseline assessment	Completed
» Medical history	Completed
» Physical / neurological examination	Completed
» Dietary treatment	Completed
» Drug / other treatment	Completed
» Neuropsychological development	-EMPTY-
» Quality of life (optional)	-EMPTY-
» MRI / MRS assessment (optional)	-EMPTY-
» Laboratory analysis	Incomplete

Patient: 001-001
Female, *03/2000 (11.25 years)

Baseline visit

Visit date: 06/06/2011 (DD/MM/YYYY)

[» Back to patients registry](#)

It is preferable to enter data of each visit in a single session. However, if this should not be possible for certain reasons (e.g. test results are pending), you could complete the forms successively. To continue with data entry for the baseline visit, please click on the **date of the baseline visit** which is found in the list of patients (see below, **red arrow**). Then you will return to the baseline visit window where you can complete the data entry. The same procedure is also possible for regular (annual) and emergency visits.

Completion of data entry

Please click on a patient for more options...

001-001, Female, * 03/2000, MMA	Regular study patient	Next regular visit in 349 days				
Basic data - Completed	Visits	Add a visit for this patient:				
Edit...	<table border="1"> <thead> <tr> <th>Visit type</th> <th>Status</th> </tr> </thead> <tbody> <tr> <td>06/06/2011 Baseline</td> <td>Incomplete</td> </tr> </tbody> </table>	Visit type	Status	06/06/2011 Baseline	Incomplete	<input type="text" value="Regular (annual) visit"/>
Visit type	Status					
06/06/2011 Baseline	Incomplete					
Loss to follow-up? More...		<input type="button" value="Add..."/>				

Other visit types

Once the baseline visit has been completed, you get the opportunity to add other visits:

- **Regular (annual) visit:** At least one regular visit is expected for each patient yearly. If more than one regular visit is planned, please also provide this additional information. To facilitate the preparation of the next regular visit, you find the information “**Next regular visit in days**” in the patient list. While getting closer to this date, the colour of this text changes from grey to orange and finally to red.
Every elective visit (in- or outpatient) for assessment of the current status (e.g. diagnostic procedures as MRI, neuropsychological testing) is to be documented as regular visit.

Basic information on registered patients

Please click on a patient for more options...					
001-001	Female	* 03/2000	MMA	Regular study patient	Next regular visit in 348 days
001-002	Male	* 11/2007	OTC	Regular study patient	Next regular visit in 310 days
001-003	Male	* 12/2010	OTC	Regular study patient	Next regular visit in 329 days
001-004	Male	* 05/1995	OTC	Regular study patient	Next regular visit in 316 days
001-005	Male	* 04/2007	IVA	Regular study patient	Next regular visit in 320 days

- **Emergency / unscheduled visit:** The most common cause of an emergency visit is infectious disease or another threatening episode leading to an impending or manifest metabolic decompensation which requires the start of emergency treatment or even hospitalisation. However, there might be other causes such as dislocation of a PEG tube leading to inadequate food intake causing catabolism.

If there is no impending or manifest metabolic decompensation, please document the visit as unscheduled clinical visit.

Unscheduled clinical visits can be either visits in emergency situations without (impending) metabolic derangement (e.g. minor laceration, seizures without metabolic derangement) or elective visits due to planned surgery (e.g. installation of PEG tube, liver transplantation).

- **Fatal disease course (visit):** If a (previously enrolled) patient dies during the course of the study, you can add a last visit summarising key information on fatal disease course.

You can choose visits from the pull down menu with the headline “Add a new visit for this patient” pressing “Add...” (red arrow). Then the new visit appears in the list of patients. This list is sorted chronologically and gives you a brief overview on previous visits and on the current status of data entry (“incomplete”, “completed”).

Add a new visit

The screenshot shows a patient record for '001-010, Male, *08/2009, PA, Regular study patient'. The 'Visits' section lists two visits: one on 10/05/2011 (Baseline, Incomplete) and one on 12/06/2011 (Emergency / unscheduled, Incomplete). A red arrow points to the 'Add...' button in the 'Add a visit for this patient:' section, which also includes a dropdown menu currently set to 'Regular (annual) visit'.

Enrolment of patients after acute metabolic decompensation or fatal disease course

The above described enrolment procedure (**written informed consent --> baseline visit --> further visits [to be added after the baseline visit]**) needs to be modified for patients who have not been diagnosed and registered before; but are diagnosed during or shortly after an acute metabolic decompensation or death. In this case, the following procedure is preferred:

- 1) Enrolment of patients after acute metabolic decompensation
 - a. **Written informed consent of parents and/or patient** (not later than the date of baseline or emergency visits)
 - b. **First emergency visit:** Please fill in correctly the date of admission, the date of discharge as well as the date of the emergency visit.
 - c. **Baseline visit:** preferably, shortly before the patient is discharged (i.e. in a stabilised metabolic condition). Note that the date of the baseline visit must not be earlier than the date at which written informed consent has been given. Please also note that the date of the baseline visit must not be later than the date of admission of the first emergency visit (the registry does not accept any visit prior to the baseline visit!). **In other words, please choose the date of admission of the first emergency visit as the date for the baseline visit, even though the baseline visit was actually performed shortly before discharge.**
- 2) Enrolment of deceased patients
 - a. **Written informed consent of parents or guardian** (not later than the date of baseline visit)
 - b. **Baseline and fatal disease visits:** Please choose the same date for both visits (the registry does not accept any visit prior to the baseline visit).

Lost to follow-up and data transfer

This screenshot is identical to the one above, showing the patient record for '001-010'. In this view, the 'Loss to follow-up?' field is highlighted, showing the date '12/06/2011' and the status 'Emergency / unscheduled, Incomplete'. A 'More...' button is visible next to this field.

In the above screenshot you find “Lost to follow up?” in the left corner at the bottom. There are various reasons why study patients could be lost during the course of the study. By clicking on “More...” a new window opens where you can choose the most appropriate cause for loss to follow-up from a pull down menu:

- **Informed consent withdrawn:** By choosing this option the patient still remains on your list but you will not be able to add data or change existing data.
- **Patient has moved to a metabolic centre which is NOT an E-IMD partner:** By choosing this option the patient still remains on your list, however, you are not allowed to add or change any information.
- **Patient has moved to another E-IMD study centre (DATA TRANSFER):** By choosing this option, the complete dataset of this patient will be transferred to another clinical E-IMD partner whom you can select from a list. The E-IMD partner to whom the dataset has been transferred will recognise the

request for transfer after opening the patient list. At the bottom of the page the transferred patient appears. Only by clicking on “Add...” the transfer will be completed and the patient will be added to the list of the new centre in charge. The previous E-IMD centre loses its access to the complete dataset.

Note:

Before transferring a patient to another E-IMD partner, **it is recommended to inform the partner in advance**. Please only start the transfer if you have received a confirmation from the other E-IMD partner. This avoids confusion and misunderstanding. However, if you have mistakenly transferred another patient (or if you should have not chosen the correct E-IMD partner), you may ask the other E-IMD partner to re-transfer the dataset. This option should only be used exceptionally!

Printouts

If you prefer to print out entered data of any registered patient, please press “**Print current form**” (if you would like to print out a single form) or “**Print all visit forms**” (if you would like to print out all forms of the current visit). You find these buttons at the bottom of the online forms.

Note:

Please do not keep printed visit documents (which contain the Pat-ID) in the patient file of your centre (which contains the name and other personal information) for the sake of data protection.

Download of documents

If you click on “**Downloads**” which you find in the left menu, you can download documents (forms, user manual) as Word or PDF file.

Export data

If you click on “**Patient registry**” and subsequently on “**Export data**” which you find in the left menu, you can download all previously entered patient data of your centre as a **.csv** file (please note that only the administrator gets full access to the datasets of all patients). This file format is compatible with numerous statistical programmes (e.g. SSPS, SAS, R). Please note that you will receive two files. The first file (**tbl_patients_[date of download].csv**) contains patient information that will not change (e.g. birthdate, disease name, start of symptoms, mode of and age at diagnosis), whereas the second file (**tbl_visits_[date of download].csv**) contains variable parameters used for prospective follow-up of study patients (e.g. anthropometrical parameters, dosages, symptoms).

3. How to use the online forms

Step-by-step approach

If you fill in the online forms, only some parameters will be visible while starting to enter data. New fields might become visible if you click on “YES” or other tick boxes that require further information. By this procedure, the form arborizes and develops sequentially by entering data. This facilitates data entry.

Example: Baseline assessment

If you choose a disease from the pull down menu, you might be asked for further specification. A specification is required for methylmalonic aciduria and propionic aciduria. For methylmalonic aciduria, please specify the correct disease type (or choose “Not yet classified”) and cobalamin responsiveness. By entering this information, the gene name and gene map locus appears automatically on the screen. Furthermore, the abbreviation “MMA” appears in the patient list – together with the patient-ID and birthdate (MM/YYYY).

Disease			
Methylmalonic aciduria			
MMA	Type: cblB	Gene name: MMAB	Gene map locus: 12q24
Cobalamin responsiveness: No			
Suspected diagnosis was confirmed by (Select one or more) <small>Note: For final diagnosis confirmation and completion of this form enzyme analysis or mutation analysis must be checked!</small>			
<input type="checkbox"/> Acylcarnitine profile in dried blood spots (MS/MS) <input type="checkbox"/> Amino acid analysis in plasma (HPLC) <input type="checkbox"/> Orotic acid in urine (HPLC) <input type="checkbox"/> Organic acid analysis in urine (GC/MS) <input type="checkbox"/> Enzyme analysis (Please fill in below) <input type="checkbox"/> Mutation analysis (Please fill in below)			
<input type="button" value="Save"/> <input type="button" value="Cancel"/> « Back to patient registry			

If results of enzyme analysis and mutation analysis are available, please click on “**Enzyme analysis**” and “**Mutation analysis**”. Two new fields will appear. By choosing predefined options from a pull down menu (e.g. “enzyme analysis was performed in”, by entering digits (e.g. “Result” of enzyme analysis) or digits and characters (e.g. “Nucleotide change” or “Protein change” in the results of mutation analysis), you can easily fill in the required information step by step. Additional information – if necessary – can be added as free text (see “Additional information (optional free text)”). Please always press the “**Save**” button at the bottom of the page before closing a form or before returning to the list of patients.

Suspected diagnosis was confirmed by (Select one or more) <small>Note: For final diagnosis confirmation and completion of this form enzyme analysis or mutation analysis must be checked!</small>						
<input type="checkbox"/> Acylcarnitine profile in dried blood spots (MS/MS) <input type="checkbox"/> Amino acid analysis in plasma (HPLC) <input type="checkbox"/> Orotic acid in urine (HPLC) <input type="checkbox"/> Organic acid analysis in urine (GC/MS) <input checked="" type="checkbox"/> Enzyme analysis (Please fill in below) <input checked="" type="checkbox"/> Mutation analysis (Please fill in below)						
Enzyme analysis						
Enzyme analysis was performed in: Fibroblasts						
Result: 0 % (of control)						
Mutation analysis						
Mutation analysis was performed using: gDNA sequencing selected exons						
Number of mutation analysis results: 2						
Results:						
No.	Nucleotide change (e.g. c.768A>G)	Protein change (e.g. p.Arg227Pro)	Status	Parental origin	Disease association	Additional information (optional free text)
1	c.556C>T	p.Arg186Trp	homozygous	father	confirmed	
2	c.556C>T	p.Arg186Trp	homozygous	mother	confirmed	

Note: Please mention all metabolic analyses that have helped to confirm the diagnosis – also if performed in a sequential way (e.g. acylcarnitine → organic acids → enzyme analysis → mutation analysis).

Validation

Missing data. If data are missing a question mark will appear in the same line (see below). If you enter a new formula, you find a question mark in each line. Please don't worry about this. As soon as you have entered appropriate data, the question marks will disappear after saving.

Medical history	
Pregnancy and delivery	
Gestational age at birth	<input type="text"/> weeks ?
Maternal medical problems during pregnancy	<input type="text"/> ?
(Pharmaco)-Therapy during pregnancy	<input type="text"/> ?
Delivery	<input type="text"/> ? <input type="checkbox"/> Prolonged delivery <input type="checkbox"/> Fever (mother)
Anthropometrical parameters at birth	
Weight	<input type="text"/> g ?
Length	<input type="text"/> cm ?
Head circumference	<input type="text"/> cm ?

Outliers. Boxes for entering numeric data in the registry have been set up with a predefined range. If you enter anthropometrical parameters, dosages, dietary treatment parameters, lab results, ICD codes etc that are considered as out of range, you will receive a **warning note**. Please **check carefully** whether you may have made a mistake. If you are sure that the entered date is correct, you will be able to save it (however, the warning note still remains).

Example: Excerpt from **Medical history**

Anthropometrical parameters at birth	
Weight	<input type="text" value="20"/> g Warning: Weight < 500 g!
Length	<input type="text" value="531"/> cm Warning: Length > 60 cm!
Head circumference	<input type="text" value="50,3"/> cm Invalid input!

The weight is below the lower limit considered as acceptable (please note that extreme low birth weight is an exclusion criteria for the E-IMD registry), whereas the length exceeds the normal range. The head circumference is inappropriate since decimal digits can be entered only by using the Anglo-American format, i.e. using a **dot** instead of a comma (the valid input for this example would have been: **50.3 cm**)

Converters and formulas

To facilitate data entry and the use of SI units, the online forms contain many converters which transform the entered data in the correct format for the registry. You find these converters in the online forms for **Physical/neurological examination** (body temperature, BMI) and **Drug/other treatment** (L-arginine, calculation of dosage per kg body weight), **Emergency treatment** (L-Arginine, L-Arginine hydrochloride 21%, calculation of dosage per kg body weight) but most of them in the **Laboratory analysis** form (pCO₂, ammonia, lactate, serum glucose, haemoglobin, total bilirubin, Schwartz formula [creatinine clearance for patients <18 years] and the MDRD formula [for glomerular filtration rate of adult patients]).

If a converter is provided in the registry, you may also choose one of two units in the paper form to fill in the value of a laboratory parameter (e.g. you can choose to document plasma ammonia using µmol/L or µg/dL).

Note:

For some calculations the **body weight** is required. Therefore, take care that for all study visits the body weight is entered correctly in the “Physical/neurological examination” respectively the “Emergency (or other unscheduled) visit” form.

Example: Excerpt from **Laboratory analysis**

If your centre uses units that are not accepted by the E-IMD registry (e.g. mm Hg for pCO₂, µg/dL for ammonia, mg/dL for lactate, or mg/dL for serum glucose), please enter these data in the light yellow boxes (**read arrows**). Entered data will be automatically converted and then will appear in the boxes on the left side. If your centre already uses units which are appropriate for the E-IMD registry, please enter these data directly in the boxes on the left side since they do not need to be converted.

Laboratory analysis		
Basic metabolic tests		
pH	<input type="text" value="7.46"/>	
Base excess	<input type="text" value="0.5"/>	mmol/L
Standard bicarbonate	<input type="text" value="23"/>	mmol/L
pCO ₂	<input type="text" value="3.333"/>	kPa
Ammonia (plasma)	<input type="text" value="840"/>	µmol/L
Lactate (plasma)	<input type="text" value="1.32"/>	mmol/L
Serum glucose	<input type="text" value="6.667"/>	mmol/L

or convert	<input type="text" value="25"/>	mmHg	←
or convert	<input type="text" value="1500"/>	µg/dL	←
or convert	<input type="text" value="12"/>	mg/dL	←
or convert	<input type="text" value="120"/>	mg/dL	←

Download forms

All online forms are also available as a .doc files which you can find at “Downloads” (see in the left menu). From our own experience it seems preferable to print out these Word files and to fill in the printed forms by hand before entering visit data to the online forms. However, this is up to you. You might prefer entering data directly to the online forms.

Note:

Please always press “Save” before moving to the next form! This prevents loss of entered data.

4. Additional information on visits and forms

For each study visit, a selection of forms is used. Some of these forms are **mandatory**; whilst some are **optional** (e.g. required only in a certain age group).

To help identify which form is required for which type of visit, the online registry provides a selection of forms for each type of visit (see “Visit data”).

Forms for baseline visits

Mandatory

- Baseline assessment
- Medical history
- Physical / neurological examination
- Dietary treatment
- Drug / other treatment
- Laboratory analysis

Optional

- Neuropsychological development (Part I + II)
- Quality of life
- MRI / MRS assessment

Forms for regular (annual) visits

Obligatory

- Physical / neurological examination
- Dietary treatment
- Drug / other treatment
- Laboratory analysis
- Neuropsychological development (at least one assessment during the course of the project)
 - Part I: Behaviour questionnaire*
 - a) Parent questionnaire (for children)
 - b) Self report (for adults)
 - Part II: Tests*
 - a) Bayley Scales of Infant Development, 2nd or 3rd edition (age 0;6-3;6 years)
 - b) Denver-II (age 1-6 years)
 - c) WPPSI-III (2;6-3;11 years)
 - d) WPPSI-III (4;0-6;11 years)
 - e) WISC-IV (6;0-16;11 years)
 - f) WAIS-IV (16;0-90;11 years)
- Quality of life (at least one assessment during the course of the project):
 - a) **PedsQL 4.0.** Pediatric Quality of Life Inventory, version 4.0 (for children at ages 8-12 years [child report] and their parents [parent report])
 - b) **WHOQOL-BREF.** The World Health Organisation Quality of Life Questionnaire – short version (for adults)

Optional

- MRI / MRS assessment (preferably one MR investigation during the course of the project)

Forms for emergency / unscheduled visits

Mandatory

- Emergency / unscheduled visit
- Emergency treatment
- Laboratory analysis

Optional

- MRI / MRS assessment

Forms for fatal disease course

Mandatory

- Fatal disease

(Note: For patients who have not been enrolled before dying the forms “Baseline assessment” and “Medical history” are also required)

Overview: Visit types and forms

	Baseline visit	Regular (annual) visit	Emergency / unscheduled visit	Fatal disease course (of a registered patient)	Fatal disease course (of a previously unregistered patient)
<i>FORMS</i>					
Eligibility (form 0)	X				X
Baseline assessment (form A)	X				X
Medical history (form B)	X	(X)*			
Physical / neurological examination (form C)	X	X			
Dietary treatment (form E)	X	X			
Drug and other treatment (form F)	X	X			
Neuropsychological development (form H) Part I – Questionnaire on behaviour (parent report, self report) Part II – Tests (BSID-II or -III, Denver-II, WPPSI-III, WISC-IV, WAIS-IV according to the E-IMD schedule)	(X)	X**			
Quality of life (form I) PedsQL, WHOQOL-BREF (according to the E-IMD schedule)	(X)	X**			
MRI / MRS assessment (form J)	(X)	(X)	(X)		
Laboratory analysis (form K)	X	X	X		
Emergency / unscheduled visit (form D)			X		
Emergency treatment (form G)			X		
Fatal disease form (form L)				X	X

* only if update is required

** at least once during the course of the project, but no more than once per year
In brackets, optional tasks for visits

4. Further comments on selected forms and items

Eligibility (form 0)

Please follow the instructions and fill in the form completely. Otherwise, the registry will not be able generate a Pat-ID which will prevent the enrolment of a new patient. Please read carefully through the definitions for “confirmed diagnosis” and “OAD or UCD highly likely”. Furthermore, please mention the exclusion criteria.

Baseline assessment (form A)

Age at diagnosis

Age at diagnosis is defined as age of the patient, when diagnosis has been suggested first by a physician resulting in the start of a specific metabolic treatment. In patients not receiving a specific metabolic treatment (e.g. in female heterozygote OTC-D), age at diagnosis is the age of the patient when diagnosis was confirmed by mutation analysis or enzyme analysis.

The following definitions are used for developmental ages:

- **Newborn:** \leq 1 month
- **Infant:** > 1 – 18 months
- **Child:** > 1.5 – 11 yr
- **Adolescent:** > 11 – 16 yr
- **Adult:** \geq 16 yr

Mode of diagnosis

The following definition is used for different modes of diagnosis:

- **Newborn screening:** MS/MS-based newborn mass screening; screened newborns are considered as having the same *a priori* risk for suffering an inherited metabolic disease.
- **Selective screening:** Metabolic screening which has been initiated due to suspicious signs or symptoms or lab results that increase the *a priori* risk for an inherited metabolic disease.
- **High-risk family screening:** Metabolic screening in born members of a family with a previously identified index patient.
- **High-risk population screening:** Metabolic screening in a population with an increased *a priori* risk (i.e. known high carrier frequency) for an inherited metabolic disease
- **Prenatal screening:** Metabolic screening during pregnancy in a family with a previously identified index patient.

Results of mutation and enzyme analysis

- **Gene name and gene map locus** (appear automatically while choosing a specific OAD or UCD)

ORGANIC ACIDURIAS

	GENE NAME (GEN MAP LOCUS)
▪ MMA	
• mut⁰ or mut⁻:	<i>MUT</i> (6p21)
• cblA:	<i>MMAA</i> (4q31.1-q31.2)
• cblB:	<i>MMAB</i> (12q24)
• cblC:	<i>MMACHC</i> (1p34.1)
• cblD (including variants 1 and 2):	<i>MMACHD</i> (2q23.2)
• cblF:	<i>LMBRD1</i> (6q13)
▪ PA:	
• Alpha chain:	<i>PCCA</i> (13q32)
• Beta chain:	<i>PCCB</i> (3q21-q22)
▪ IVA:	<i>IVD</i> (15q14-q15)
▪ GA1:	<i>GCDH</i> (19p13.2)

UREA CYCLE DEFECTS

- **NAGS deficiency:** *NAGS* (17q21.31)
- **CPS1 deficiency:** *CPS1* (2q35)
- **OTC deficiency:** *OTC* (Xp21.1)
- **Citrullinemia type I / ASS deficiency:** *ASS1* (9q34.1)
- **ASL deficiency:** *ASL* (7cen-q11.2)
- **ARG1 deficiency:** *ARG1* (6p23)
- **HHH syndrome / ORNT1 deficiency** *ORNT1* (13q14)

• **Mutation analysis**

- Mutation analysis was performed using (analyses are on genomic DNA level unless specified otherwise):
 - gDNA Sequencing coding region (all coding exons plus adjacent introns [minimum 20nt])
 - gDNA Sequencing non-coding region (e.g. promoter, untranslated regions, introns),
 - Deletion/duplication analysis (e.g. MLPA, for detection of large deletions or duplications)
 - cDNA sequencing (sequence analysis of mRNA transcripts obtained from cell lines)
 - Next-generation sequencing
 - gDNA Sequencing selected exons (targeted analysis of exons containing common mutations; limited sensitivity)
 - Mutation screening (targeted analysis of specific [common] mutations; limited sensitivity based on population background)
 - Mutation scanning (indirect for identification of genetic variants; limited sensitivity based on method)
 - Unknown method
- Results of mutation analysis (complete the table):

No.	Nucleotide change	Protein change	Status	Parental origin	Disease association	Additional information
1	<i>Fill in</i> (e.g. c.768A>G)	<i>Fill in</i> (e.g. p.Arg227Pro)	<i>Choose one:</i> heterozygous, homozygous, hemizygous, mosaic	<i>Choose one:</i> father mother unknown new mutation	<i>Choose one:</i> confirmed likely no unknown	<i>Add free text</i>
2						
3						
4						
5						
6						

- **Residual enzyme activity**

- Enzyme analysis was performed in (*choose one*):

- Leukocytes
- Erythrocytes
- Fibroblasts
- Liver
- Small intestine

- _____% of control (*do not fill in, if MMA is chosen as diagnosis*).

This field will not appear in the database, if MMA was chosen as diagnosis on the prior page.

- MMA (*fill in appropriately, if MMA is chosen as diagnosis*).

If you have chosen MMA as diagnosis on the prior page, following boxes (as shown below) will appear. You do not need to fill in every box, as **different forms of MMA (isolated/combined) require specific biochemical examinations. Even if some boxes should remain empty, the form in the database can be saved and its status will be set to “complete” nevertheless.**

Propionate fixation: with OH-Cbl _____ % (*mean of control*)

without OH-Cbl _____ % (*mean of control*)

Mutase activity: with Ado-Cbl: _____ % (*mean of control*)

without Ado-Cbl: _____ % (*mean of control*)

Methionine synthesis: with OH-Cbl _____ % (*mean of control*)

without OH-Cbl _____ % (*mean of control*)

Complementation analysis: _____ (*enter free text*)

Adenosyltransferase activity: _____ (*enter free text*)

Medical history (form B)

Maternal medical problems during pregnancy

If you select "YES", you will be asked for further specification.

Delivery

Please check only one mode of delivery. If more than one applies, please check the most invasive one by going down the list (e.g. if delivery was induced at first and then vacuum extraction was necessary, check "vacuum extraction", since it is considered the more invasive of both methods).

Postnatal problems

If you select "YES", you will be asked for further specification.

Clinical presentation

Please decide if the patient is symptomatic or asymptomatic. A patient is symptomatic if he or she shows symptoms associated with or leading to the respective diagnosis. If the patient is symptomatic please enter the age the symptoms manifested for the first time. A patient that is asymptomatic at enrolment can turn symptomatic during the course of the project, in this case please update the status in form B.

If applicable, fill out the rest of this subsection to capture the first metabolic crisis of the patient. Please enter the laboratory parameters that reflect the point of maximal metabolic derangement, even if a specific treatment has already been started (e.g. fill in the maximum plasma ammonia concentration which has been documented during the metabolic crisis). In some cases laboratory parameters reflecting the point of metabolic derangement might be determined at different points of time (e.g. plasma for amino acids taken shortly after admission of the patient, maximum ammonia measured a few hours later). However, they can be used to describe the metabolic derangement if the time span is within hours.

Kindergarten/school/professional

Please refer to the current state and previous history.

Example: An adult patient with GA-I is employed as controller after having studied economics and having passed regular school and kindergarten. Please fill in this information as follows:

Kindergarten / school / professional career	
Attends / Attended ...	
Kindergarten	Yes <input type="checkbox"/> ?
School	Regular school <input type="checkbox"/> ?
Professional training	Student <input type="checkbox"/> ? for Economics <input type="text"/>
Employment	Yes <input type="checkbox"/> ? as Controller <input type="text"/>
Unemployed	No <input type="checkbox"/> ?

Social history

Please refer to the current state only.

Metabolic follow-up

Emergency card

The "emergency card" is meant to be a document including basic information on the patient, the disease, emergency treatment and the telephone number of a metabolic centre. It may be a credit card-like piece of paper. The individual treatment plan is not meant by this.

Contacts to patients with the same disease: Please choose the most appropriate answer.

- **"Patient does not know and does not have any contact to other patients"** (with the same disease): this also includes other family members of another patient with the same disease
- **"Patient knows other patients"** (with the same disease): For example: he/she has met another patient incidentally (e.g. in the outclinics) but does not meets other patients planned in advance.
- **"Patient meets other patients regularly"**: ...and planned in advance.

- **“Patient is [active] member of a patient support group”**: Being an active member also includes having contact and meeting other patients regularly and planned in advance. Please note, that this option is only applicable if the support group in question is focused on the respective metabolic disease of the patient, thus enabling the patient to meet other patients with the same disease.

Physical / neurological examination (form C)

Historical note (recent year/since last regular visit)

You are asked to give information about occurrence and frequency of diarrhoea, vomiting and seizures since the the last regular visit or in the recent year (in case of first study visit or if the last visit has been more than one year ago). In case of first regular visit, historical note refers to the time span between base line visit and time of first regular visit. Please do not state any of these episodes if they are documented as part of an emergency (ER) visit.

Six gross motor development milestones

Choose the most advanced gross motor development milestone of the patient even if another milestone which is usually achieved earlier has not yet been achieved (e.g. fill in hands-and-knees crawling in a patient who shows crawling but cannot yet sit without support).

Liver size

If you should note clinical abnormalities of liver size or localisation in a patient with a liver transplant, please check “not examined” and give a diagnosis utilizing ICD-10 codes.

Technical investigations

Some technical investigations are recommended to be performed for some patient groups in given time intervals. For example, heart ultrasound should be done once a year in OAD patients.

Liver ultrasound should be performed in patients with clinical signs of hepatomegaly. Of course also in other situations liver ultrasound may be appropriate, e.g. in the follow up of known liver fibrosis.

Technical investigations conducted up to 2 weeks prior to, or after a given regular visit, can be entered as part of that visit, provided that there weren’t any clinically relevant changes in the clinical status or treatment of the patient. Technical investigations not fitting into this time window should be documented as separate regular visits. Please note that this procedure does not apply to Emergency visits, in this case only technical investigations which are part of the current hospitalization should be entered as part of the corresponding emergency visit.

Specification of non-metabolic diseases

For all non-metabolic diagnoses please use **ICD-10** (international statistical classification of diseases and related health problems, 10th revision, version for 2007) codes.

A **tabular list of ICD-10** is available online at: <http://apps.who.int/classifications/apps/icd/icd10online/>

Please enter diagnoses that refer to clinical abnormalities which you have previously mentioned in the physical or neurological exam paragraphs but also signs and symptoms that are not explicitly asked for in the online form (e.g. skeletal and ophthalmological disorders). When performing a regular visit, clinical abnormalities that have been noted in a previous baseline, regular or emergency/unscheduled visit should be entered again if they still persist at the time of the current regular visit.

After entering the ICD-10 code and pressing “Save” the ICD-10 label appears in the same line. This text allows you to validate the correctness of the entered code.

Example: If you enter the code **“A08.0”**, the label **“Rotaviral enteritis”** will appear after saving.

Dietary treatment (form E)

Calculated diet

Choose “YES”, if this patient has a dietary treatment plan with clearly defined daily intake of protein (natural protein, amino acid mixture, and single amino acid supplementation) and calories. Choose “NO”, if this patient does not follow any diet at all or whether he/she solely reduces the intake of protein-rich food (without calculation).

If a patient does not follow the recommended dietary treatment plan, you should choose “avoids protein excess” or even “no diet” instead of “calculated diet”.

Drug / other treatment (form F)**Drug therapy**

If body weight is provided (in “Physical / neurological examination”), the weight-related dosage will be automatically calculated.

If a medication is applied once in a given period of time, please calculate the dosage per day (e.g. hydroxycobalamine 3 mg/ week → 0.43 mg/day). Colistin and metronidazole are an exception to this rule. In the case of these two drugs you should specify the number of days per month a patient has received this medication and record the amount given on a single day.

If necessary, please add further medication by mentioning the **active agent** and calculating the dosage per day as described above.

If a medication is applied on demand, please add “**PRN**” (pro re nata) after the drug’s name (e.g. melatonin PRN, 2 mg).

Extracorporeal detoxification

Please specify the method and frequency of extra-corporal detoxification used.

Transplantations

Please specify the organ transplantation and the date of transplantation (also if re-transplantation was required).

Neuropsychological development (forms Hi and Hii)

Part I: Behaviour questionnaire (form Hi, parent report and self report)

The behaviour questionnaire should be filled in during an interview with the parents (parent report) and/or the patient (self report). The interviewer has a form of understandable questions that translate the terminology of behavioural problems into layman's language. The questionnaire focuses on the quality of behavioural abnormality as well as on its intensity, frequency and its effect on family life. If for some reasons some of the items couldn't be answered please chose the option "data missing".

Patients younger than 5 years are not assessed with the behaviour questionnaire, patients aged 5 years but younger than 13 years are assessed with the parent report; patients aged 13 years and older are assessed with the self report. If the capabilities of a patient of eligible age are not sufficient for the self report you should use the parent report instead. For patients of eligible age the behaviour questionnaire should be administered once per year starting with the baseline visit.

Behaviour questionnaires administered up to 2 weeks prior to, or after a given regular visit, should be entered as part of that visit, provided there weren't any clinically relevant changes in the status or treatment of the patient. Behavioural questionnaires not fitting into this time window should be documented as separate regular visits.

Part II: Test results (form Hii, separate print forms are available for all tests used for E-IMD)

During the course of the study neuropsychological testing should be performed at specific ages. Tests should be performed according to the following time schedule (see below).

Note:

Any patient should be tested at the baseline visit if he/she is 12 months or older. Please assign the test battery which is most appropriate for your patients' age and capabilities and continue according to the schedule. E.g. if a patient is enrolled at the age of 39 months the test battery for the 36 months time point would still be appropriate for the baseline testing and the next time point for testing would be 5 years.

E-IMD test schedule

Testing age	Tests
<i>For patients 12 months and older at baseline visit</i>	<i>choose battery appropriate to current age</i>
1;0 (1;0 – 1;2) year	BSID-II or III (cognitive scale) + Denver II
2;0 (1;10 – 2;2) years	BSID-II or III (cognitive scale) + Denver II
3;0 (3;0 – 3;2) years	WPPSI-III + Denver II
5;0 (4;6 – 5;6) years	WPPSI-III
8;0 (7;6 – 8;6) years	WISC-IV
15;0 (14;6 – 15;6) years	WISC-IV
18;0 (17;6 – 18;6) years	WAIS-IV

BSID-II, Bayley Scales of Infant Development, second edition
BSID-III, Bayley Scales of Infant Development, third edition
Denver II, Denver Developmental Screening Test ("Denver Scale"), second edition
WAIS-IV, Wechsler Adult Intelligence Scale, fourth edition
WISC-IV, Wechsler Intelligence Scale for Children, fourth edition
WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence, third edition

Note:

In any case the patient could not be examined with the test appropriate for age, try to apply the test for younger age groups. At least try to rate the developmental age by asking parents/carers to rate the items of the Denver Developmental Screening Test ("Denver Scale").

If patients have been testable, characteristic test results are entered in the online forms.

Psychological tests conducted up to 2 weeks prior to, or after a given regular visit, should be entered as part of that visit, provided there weren't any clinically relevant changes in the status or treatment of the patient. Psychological tests not fitting into this time window should be documented as separate regular visits.

Quality of life (form I)

Assessment of quality of life follows standard QoL questionnaires

- a) **PedsQL 4.0** (for children from ages 8-12 years [child report] and their parents [parent report])
- b) **WHOQOL-BREF** (for adults)

E-IMD schedule for QoL assessment

Age	Quality of Life (patients)	Quality of Life (parents)
8 – 12 years	PedsQL (child report)	PedsQL (parent report for children)
13 - 17 years	PedsQL (child report)	PedsQL (parent report for children)
18+ years	WHOQOL-BREF	

*If a patient is enrolled between age 8 and 12 years, please start with QoL assessment at the baseline visit.

Patients of eligible age should be assessed no more often than once per year with the appropriate questionnaire according to the above schedule. If a patient is enrolled at the age of 8 or older start the assessment with the appropriate questionnaire at the baseline visit.

Note that the numbering of the online forms is in accordance with the numbering of the original PedsQL and WHOQOL-BREF questionnaires. As stated on the quality of life questionnaires, the last four weeks should be considered by the patient and the parents. In case of short term afflictions not related to the underlying disease (i.e. trauma, infectious diseases), please encourage the participant and the parents to report the quality of life for a representative period of time.

Quality of life questionnaires administered up to 2 weeks prior to, or after a given regular visit, should be entered as part of that visit, provided there weren't any clinically relevant changes in the status or treatment of the patient. Quality of life questionnaires not fitting into this time window should be documented as separate regular visits.

MRI / MRS assessment (form J)

Please follow the instructions on the online form. All required information can be selected from pull down menus.

Laboratory analysis (form K)

Since different units are still used worldwide, this form needs some attention. **Please take care that you enter lab results using units that are acceptable for the E-IMD registry!** Various **converters** help you to convert your lab results in appropriate units.

For metabolic analyses, some items are tailored, e.g. a box for "Methylmalonic acid" is only provided for patients with methylmalonic aciduria. However, the majority of biochemical parameters are the same for all patients. Accordingly, you may identify single parameters that you judge as unsuitable for the follow-up of patients with certain diseases (e.g. plasma ammonia in glutaric aciduria type I). Therefore, although all forms should be filled in as completely as possible, you may decide to cancel single biochemical parameters for certain diseases if you judge them as unusual or inappropriate. Please inform the administrator if you plan to neglect certain parameters systematically.

With respect to acylcarnitines (C0, C3, C5, C5DC) you are given the option of entering values measured either in dried blood spots or plasma. If your laboratory is able to provide both methods, please enter acylcarnitines measured in dried blood spots preferably.

In case of emergency visits (**ER**) please enter the laboratory parameters of the maximal metabolic derangement before a specific emergency treatment has been started.

If you can't give an exact value for a laboratory test, because the result is beneath or above the respective cut-off level, please enter the cut-off level with the last place lowered or raised by one respectively (e.g. Amylase <5, enter 4; CRP <2.0, enter 1.9). "Amylase" only asks for pancreas amylase.

Emergency / unscheduled visit (form D)

The forms of the emergency / unscheduled visit are a compilation of forms and items which are also used for the regular (annual) follow-up. In addition, you find a paragraph on putative triggers of metabolic decompensation.

If the visit qualifies as emergency visit and one or more triggers can be identified please check “yes” and fill in this part. If no trigger can be identified, please check “no”. If the visit is an unscheduled clinical visit please check “not applicable”. Please state the diagnosis detected during the emergency or other unscheduled visit as ICD-10 code at the end of form D if appropriate (“**Specification of non-metabolic diagnoses**”). As opposed to Form C please refrain from entering diagnoses which already have been noted at a prior visit and are persistent. Limit yourself exclusively to those clinical abnormalities which haven been detected the first time at the emergency or unscheduled clinical visit at hand and/or are the cause for this emergency or unscheduled clinical visit.

For differentiation of emergency visit and unscheduled clinical visit, please see above (“2. How to use the patient registry, Other visit types”).

Visit date

Please note that a visit date before the date of discharge (if hospitalisation has been required) will not be accepted. The reason for this is that you might not have some of the required information before the day of discharge (e.g. clinical consequences of the ER visit / hospitalisation).

Emergency treatment (form G)

Please mark “emergency treatment started at home” if changes in diet (e.g. protein reduction) or medication (e.g. increase of carnitine dosage, start of antipyretic treatment) have been performed before hospital admission.

If the visit is documented as unscheduled visit, please refrain from filling in the emergency treatment form, since the explicit purpose of this form is to capture only the treatment of acute metabolic decompensations. Check the not applicable field instead.

Drug therapy and dietary management

In case of an emergency visit, please only refer to the **starting dose** of drug therapy and dietary management for an individual patient. Any subsequent changes (increased or decreased dosages) of metabolic emergency treatment cannot be entered. The reason for this is that subsequent changes are highly variable and individualised so that appropriate statistical analysis of these variations seems impossible.

Fill in the complete initial treatment, metabolic as well as non-metabolic, including the treatment imposed due to the underlying cause of acute illness and the continued chronic treatment.

Note:

A metabolic decompensation might result in a permanent adaptation of the long-term metabolic management (dietary treatment, pharmacotherapy) of this patient. If this happens following an emergency visit of a patient, please capture these changes by adding a regular visit and by entering the adapted permanent treatment protocol at the end of the emergency visit. The date of this regular visit should be the day of discharge.

For sodium benzoate, sodium benzoate/sodium phenylacetate, L-arginine hydrochloride 21% and L-carnitine you can enter the amount given as initial bolus separately.

In case of application of Ammonul™ (Sodium benzoate/Sodium phenylacetate), please fill in the dosage of only one active agent and do not add both ingredients.

Ammonul™ consists of an equimolar solution of sodium benzoate and sodium phenylacetate.

For example, applying Ammonul™ 100 mg per day means that the patient receives 100 mg of sodium benzoate and 100mg of sodium phenylacetate per day. In this case please document Ammonul™ 100mg/d in forms and database.

Fatal disease course (form L)

Date and (known or suggested) cause of death should be stated. A selection of putative causes is provided by a pull down menu. If a cause is suggested/ identified which is not mentioned on the list, please add this by using "other causes" and by specifying the ICD-10 code.

If the manner death was suicide, please fill in "Suicide" in "other causes".

Trouble shooting, fault management and training

If you identify a mistake or a problem, would like to suggest a change for improving the registry or do not properly understand the function of the registry and its tools, please contact us directly. You can use the contact form or send an e-mail to the administrators (Stefan.Koelker@med.uni-heidelberg.de; Peter.Burgard@med.uni-heidelberg.de). We will try to solve your problem asap.

For those who prefer personal training in data entry and management, please do not hesitate to contact the Heidelberg team. We are happy to offer you practical training in our centre (1-2 days).