UNITED FOR METABOLIC DISEASES
Plan van Aanpak: Jaar 1 t/m 5 (2019-2023)

United for Metabolic Diseases

United for Metabolic Diseases (UMD) is een zelfstandig, multidisciplinair en translationeel samenwerkingsverband voor onderzoek aan metabole ziekten. Het verbindt het klinisch en basaal onderzoek van de zes landelijke universitaire metabole expertise centra en patiëntenvereniging 'Volwassenen en Kinderen met Stofwisselingsziekten'(VKS). Het UMD heeft als doel om de diagnostiek, behandeling en zorg voor patiënten en gezinnen met een erfelijke metabole ziekte te versnellen en te verbeteren. Dit door betere registratie, preventie, zorg, educatie, opheldering en begrip van de pathofysiologie, en therapieontwikkeling. Door bundeling van de bestaande kennis en expertise op het gebied van erfelijke metabole ziekten, het uitvoeren van innovatief fundamenteel en toegepast onderzoek , en het vertalen in nieuwe klinische toepassingen, zal ons samenwerkingsverband zowel nationaal als internationaal een leidende rol spelen in het garanderen van een verbeterde toekomst voor alle patiënten en gezinnen met erfelijke metabole ziekten. De oprichtingsbijeenkomst vindt plaats op 5 februari 2019.

Algemene doelstellingen van het UMD

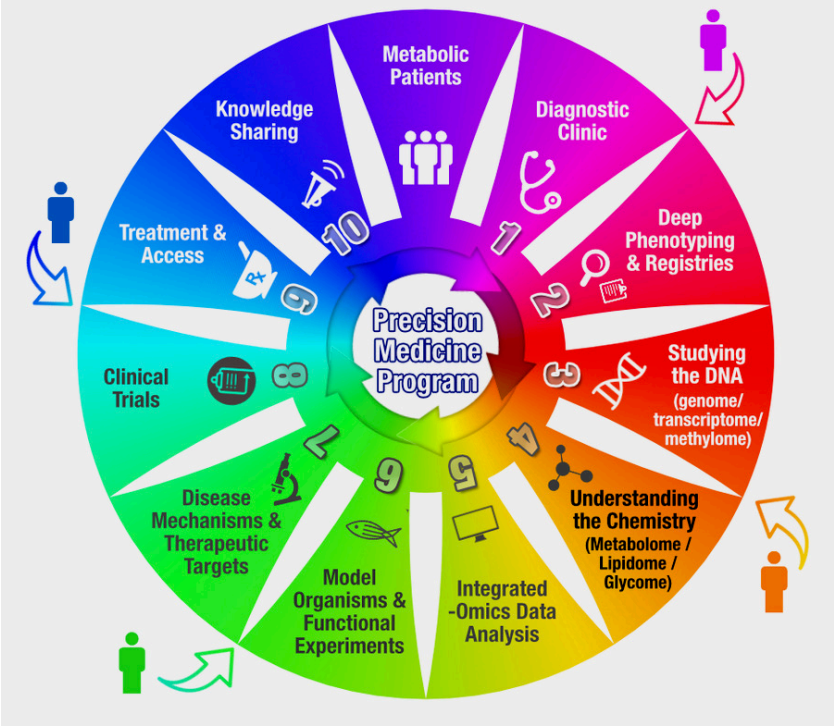
1. Het efficiënt stellen van precieze diagnoses bij patiënten met erfelijke metabole ziekten, zo snel en vroeg mogelijk in het beloop van de ziekte.
2. Het identificeren en karakteriseren van nieuwe erfelijke metabole ziekten en nieuwe klinische presentaties van bekende aandoeningen, alsmede het verzamelen van *natural history* data om het beloop van de ziekte vast te kunnen leggen.
3. Het genereren van nieuwe kennis van ziektemechanismen en factoren die het beloop van de aandoeningen bepalen en beïnvloeden, om therapeutische targets te identificeren en prognoses en de juiste timing van interventies te kunnen optimaliseren.
4. Het identificeren van biomarkers voor prognose en om de respons op therapie te kunnen monitoren en voorspellen.
5. Het ontwikkelen van nieuwe behandelingen en nieuwe toepassingen van bestaande behandelingen, het uitvoeren van klinische trials en het optimaliseren van toegang tot therapie en behandeling.
6. Het faciliteren van *clinical research and trial units* om zorg op maat te kunnen verrichten en gedetailleerd het effect van interventies (nieuw dieet, voedingssupplement, medicatie) vast te kunnen leggen.
7. Het verspreiden van kennis omtrent erfelijke metabole ziekten met als doel eerdere herkenning en een brede maatschappelijke erkenning.

5 jaren doelstellingen van het UMD

Het streven van het UMD voor de eerste 5 jaar is minimaal de volgende resultaten te behalen:

- Grotere bekendheid rondom erfelijke metabole ziekten in NL met de mogelijkheid tot vroege verwijzing naar de *Solve the Unsolved Clinic*, waarin ~500 patiënten uitgebreid onderzocht worden. Hierbij worden naar verwachting 250 diagnoses gesteld, waarvan 25 nieuwe aandoeningen.
- Multidisciplinaire spreekuren: waarin patiënten in een consult door verschillende experts gezien zullen worden, wat leidt tot versnelling van diagnostiek, meer gerichte therapie en minder ziekenhuisbezoeken, maar ook tot directe uitwisseling van kennis en inzichten tussen behandelaars.
- Verbeterde landelijke registratie en documentatie van patiënten met metabole ziekten.
- Nieuwe inzichten in de pathofysiologie van metabole ziekten.
- Ontwikkeling van nieuwe toegepaste therapieën en optimaliseren van bestaande therapieën voor verschillende erfelijke metabole ziekten.
- Betere toegankelijkheid van bestaande en nieuwe therapieën voor metabole ziekten.
- Het direct vertalen en verspreiden van kennis omtrent erfelijke metabole ziekten, zodat patiënten, hun familie, de gezondheidsprofessionals, en de samenleving direct profijt hebben van het UMD.
- Wetenschappelijke en publieke presentaties en artikelen, instrumenten voor training en voorlichting op het gebied van nieuwe ontwikkelingen binnen de erfelijke metabole ziekten voor diverse klinische specialisten en laboratorium medewerkers
- Ontwikkeling van het UMD tot duurzaam samenwerkingsverband met actieve participatie van patiënten en families

Om onze doelen te bereiken hebben we verschillende activiteiten geidentificeerd, die de verschillende spaken van het onderstaand vliegwiel vormen.



De patiënt kan in iedere spaak van het vliegwiel, of wel fase van het programma worden opgenomen, waarvan het verbeteren van de gezondheidsuitkomst het uiteindelijke doel is. Dit betekent inclusie van patiënten: 1) zonder diagnose, 2) met een vastgestelde erfelijke metabole ziekte maar zonder mogelijke behandeling, of 3) met behandeling maar met onvoldoende positief resultaat. Het doel is om de patiënt verder door deze cirkel te doen bewegen, in de richting van behandeling en zorg op maat. In het **UMD** zijn de expertise en ervaring bijeengebracht om patiënten deze stappen te laten doorlopen en wetenschappelijke inzichten toepasbaar te maken in de dagelijkse praktijk zodat deze ziektes beter herkenbaar en behandelbaar worden.

Work packages binnen het UMD Om onze doelstellingen te bereiken zijn vijf work packages gedefinieerd. Deze worden aangestuurd door een work package coördinator en hebben eigen (deel)doelstellingen en 'taskforces'. Deze worden hieronder beknopt in het Engels toegelicht.

Work package 1. Knowledge and data sharing

Work package coordinator: Dr. Terry Derks (UMC Groningen)

Overall aim of work package

The overall aim of this work package is to improve outcomes for patients with inherited metabolic diseases by increasing awareness, providing education, strengthening patient registries, and enhancing knowledge translation and dissemination. We aim to establish a national metabolic **Care Continuum Model**, characterized by full integration of education, research, telemedicine, home monitoring of big data (including the diet), patient care, and patient-clinician-research collaborations.

Specific objectives

1.1 To establish a digital National Registry for metabolic patients providing accurate overview of living and deceased patients

1.2 To develop on-line e-learning modules to promote dissemination of knowledge and training on inherited metabolic diseases

1.3 To design one metabolic e-health platform for patients to support data sharing between patients and health care providers

1.4 To integrate virtual counselling by means of a CPMS (Clinical Patient Management System) to support sharing of expertise, improved second opinions and application of expert knowledge

Work plan in brief per objective (including provisional time line)

1.1 Development of a new format for current DDRMD in collaboration with specialized IT companies (year 1), transfer data from current DDRMD and expand with lacking patient data (year 2 and further). Requires participation of metabolic clinicians, patient organizations, legal advice, maintenance fee etc. Data acquisition by clinical coordinator(s).

1.2 Includes collection of national metabolic e-learning experiences and existing e-learning programs, designing a case format and workflow (year 1), developing modules and defining accreditation requirements (year 2 and further). Can be performed by pediatrician fellows metabolic diseases; requires IT input.

1.3 Includes collection of national metabolic e-health experiences, identification of relevant patient reported evaluation and outcome measures (year 1), development of individual care pathways for metabolic disorders (year 2 and further). Requires IT expertise, legal advice, input of patient organizations, maintenance fee etc. Data acquisition and maintenance by nurse practitioners, dieticians, pediatrician fellows metabolic diseases.

1.4 Includes pilots and connection between EC, OpenApp and UMC's, CPMS feedback from end users, designing a formal second opinion pathway, video consulting with patients and video consulting or webinars with groups of patients about specific topics. Requires

IT expertise, participation of metabolic clinicians, input of patient organisations, legal advice, maintenance fee etc. Will not be initiated in first year.

Challenges and Mitigation Strategy

- Our activities will require collaborations and interconnectivity between platforms (including electronic health records within the UMCs), devices and databases. In order to obtain a most efficient and less time-consuming flow it should be considered to contract data managers, and generate one care portal (*zorgportaa*l) or ICT-platform to translate generic published guidelines and care pathways into metabolic-specific personal health files.
- Inter-UMC and Health Care Provider-patient data sharing may be complicated due to legal, privacy, ethical, and liability issues. It will be challenging to find a good balance between interests of the UMCs/NFU and the UMD. The UMD will need legal advice on this point.
- Patient participation in (sponsor and investigator initiated) clinical research can be improved if the research protocols, patient information letters and informed consent letters are produced in collaboration with a patient expert panel.
- The number of metabolic specialists in the Netherlands is too small. For this reason in the upcoming years, it would be advisable to involve clinical/laboratory fellows metabolic diseases in the care/ research elements per WP to expand and support existing metabolic teams and enhance successful delivery of milestones.

Impact for the field of inborn errors of metabolism, UMD, science and society

Improved awareness, registration and outcomes for patients with metabolic diseases as well as the caregivers, health professionals and Researchers involved.

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Work package 2. Technology development

***Work package coordinator*:** Prof. dr. Dirk Lefeber (Radboudumc Nijmegen)

Overall aim of work package

WP2 aims to develop and deliver key technologies required for the UMD, including bioinformatic solutions for the combined interpretation of available -omics data, cellular fluxomics for diagnostics and therapy studies, and patient-derived stem cell models to test therapeutic strategies for metabolic diseases. WP2 will be actively involved in collaborations with existing initiatives on biomarker and integrated omics technologies such as the Netherlands Metabolomics Center, X-Omics, SOLVE-RD and RD-Connect, as well on stem cell technology such as the HDMT.

Specific objectives

1.1 To develop and/or build infrastructure for storage, integration and exchange of –omics data
1.2 To develop analytical and bioinformatics methodologies to study metabolism in patient derived blood (cells) and (stem) cell models to identify biomarkers, study pathophysiology and design therapeutic strategies
1.3 To develop cellular fluxomics techniques for diagnostics and therapy studies
1.4 To share and develop hiPSC technology for metabolic disease research
1.5 To generate a national inventory on metabolic research expertise

Work plan in brief (including provisional time line)

1.1 To make a national inventory for needs and requirements in order to develop a data management plan on the sharing and storage of -omics data. Establish collaboration with other national initiatives on –omics data integration and sharing. Requires IT expertise, bioinformaticians, data stewards, legal advice, infrastructure costs, big data storage, maintenance fee etc.
1.2 Application of metabolomics, lipidomics and glycoproteomics in clinically well-defined cohorts of known metabolic disease patients. To develop optimal technology, the UMCs will contribute material from 2-3 metabolic disease groups for analysis, which will be analyzed by different –omics technologies followed by bioinformatic analysis of data to group patients and identify potential (clusters of) biomarkers.
1.3 Unite groups from different UMDs to further develop isotope-based flux analysis methodologies to study metabolism in patient derived blood cells, cultured primary cells and (stem) cell models to identify biomarkers, study pathophysiology and therapeutic strategies. Requires laboratory specialists, researchers and bioinformaticians.
1.4 Develop and disseminate technology for gene editing in hiPSCs and differentiation protocols to target tissues that are relevant for metabolic disease patients.
1.5 Make an inventory of the scientific expertise and technologies that are present within the participating centers of the UMD. These include genetic, biochemical, analytical, molecular and cell biological expertise, technologies and model systems. The aim is to make these technologies known and available to the UMD participants. Two working

groups will execute this task, one for –omics technologies (Fred Vaz, Dirk Lefeber) and one for stem cell technologies (Pim Pijnappel, Sabine Fuchs).

Challenges and Mitigation Strategy

- Within UMD alone there is insufficient man power, know-how, legal knowledge and funds to develop infrastructure for storage, integration and exchange of –omics data. It will be essential to team up and collaborate with other initiatives and IT companies with similar goals.
- Within UMD alone there is insufficient man power, know-how, legal knowledge and funds to develop stem cell models to study metabolic disease. It will be essential to team up and collaborate with other initiatives, especially to embed metabolic disease in ongoing national initiatives such as HDMT.

Impact for field of inborn errors of metabolism, UMD, science and society

Groundbreaking technological innovation to enable efficient diagnosis and management of patients with inherited metabolic diseases, as well as improved insight into pathophysiology and therapeutic development and application

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Work package 3. Solve the Unsolved

Work package coordinator: Prof. dr Nanda Verhoeven - Duif (UMC Utrecht)

Overall aim of work package

Identification of the genetic and biochemical basis of unexplained phenotypes suspicious for a metabolic disease in whom standard care and routine clinical diagnostics did not yield a conclusive diagnosis. This will result in the identification and characterization of novel metabolic diseases, genes, phenotypes, pathways and/or novel functions thereof, and the unravelling of pathophysiological mechanisms to enable implementation or development of therapeutic options.

Specific objectives

1.1 Establish METC protocol for inclusion of patients in UMD

1.2 Inclusion of 500 patients with an unexplained phenotype suspicious for a metabolic disorder based on well-defined but broad inclusion criteria

1.3 To study how untargeted metabolomics and whole exome/genome sequencing complement each other in diagnosing rare disease, including development of integrated interpretation of –omics data (with WP2)

1.4 Analysis of patients using defined sets of –omics techniques to identify underlying cause

1.5 Analysis of selected patients using specific –omics tests

1.6 Application of functional studies (genetic, biochemical, analytical, molecular and cell biological) in various cell models to study function of novel genes and pathogenic consequence of mutations in genes (see also WP2 1.5)

Work plan in brief (including provisional time line)

1.1 An elaborate ethical protocol for inclusion of patients in the UMD program will be written with input of clinical and laboratory partners and submitted for evaluation to the METC of the Amsterdam UMC, location AMC (year 1). Upon acceptation, the protocol will be submitted to the METCs of the other UMCs. Requires participation of metabolic clinicians, geneticists, laboratory experts, clinical coordinator.

1.2 We aim to include in 5 years ~500 patients (any age/gender/background) with an unexplained phenotype despite extensive standard of care clinical work-up, but suggestive of an IEM. Patients will be referred from all participating University Medical Centers in the Netherlands at the following outpatient clinics: pediatrics, internal medicine, neurology, clinical genetics and psychiatry. Clinical history and work-up of potential patients will be assessed by a panel of metabolic clinical and laboratory experts and may initially include advice for further diagnostic work-up before inclusion. Requires participation of metabolic clinicians, fellows metabolic diseases, laboratory experts, clinical coordinator(s).

1.3 A selected set of patients with different metabolic diseases will be analyzed by whole exome/genome sequencing and untargeted metabolomics using different matrices (whole blood, plasma, blood spots, cells) followed by analysis and integration of the

data. Such efforts have already been initiated in Utrecht and Nijmegen and will be expanded and coordinated. Requires bioinformatics expertise, big data storage capacity and participation of laboratory experts, clinical coordinator(s), bioinformaticians.

1.4 Patients who meet the inclusion criteria (see 1.1) will be subjected to a standardized set of -omics analysis, including whole exome sequencing and untargeted metabolomics in blood spots, plasma and/or whole blood (to be determined at 1.2) to identify the underlying genetic and/or biochemical cause

1.5 Patients who remain without a conclusive diagnosis after 1.3 or suspected for specific defects based on 1.3 data will be subjected to specific –omics analysis, including lipidomics, glycomics, transcriptomics, epigenetic analysis. Requires bioinformatics expertise and participation of laboratory experts, clinical coordinator(s), bioinformaticians.

1.6 Apply the functional genetic and metabolic expertise and technologies present and available within the participating centers of the UMD (inventory at 1.5; WP2) to study functions of (novel) genes and consequences of deletions thereof or specific patient mutations, as well as create models for therapy development/evaluation. These include different genetic, biochemical, analytical, molecular and cell biological technologies as well as model organism and cell lines studies.

Challenges and Mitigation Strategy

- Number of patients that can or will be included. Will be important to develop well-defined but broad inclusion criteria, to actively inform health care providers inside and outside of the metabolic community about this initiative.
- Sufficient and timely bio-informatics capacity to enable development of integrative multi-omics diagnostic approaches. To develop bio-informatic tools, it will be important to team up with other national/international consortia that also work on similar approaches.
- Sufficient time and human capacity in the metabolic laboratories to support/drive this program. The laboratory staff and personnel required to run this program, will not be paid directly by the UMD and may be limited in time and capacity (allowed) to participate in it. It is essential that the administrations of the UMCs are aware of the importance of this approach and feel the need to invest in it.

Impact for field of inborn errors of metabolism, UMD, science and society

Diagnosis of a metabolic disorder can be a major challenge because of rarity and phenotypic heterogeneity of the individual disorders and complex diagnostic tests that take long when performed sequentially. As a result, individuals suffering from IEM undergo lengthy diagnostic trajectories of often over a decade and suffer health loss that may be prevented or ameliorated by timely diagnosis. A diagnosis is of great importance as it provides an answer to patient and family and ends the diagnostic odyssey. A prognosis may be given, and therapeutic options and community services may be available. It also enables accurate

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genetic counselling on recurrence risk with options of prenatal diagnosis and pre-implantation genetic diagnostics and identification of family members at risk. A diagnosis sets the stage for future intervention and better preventive management and overall care. The field of inborn errors will be boosted by this project as all centers will participate, we will share knowledge and we will learn a lot as the field increases in activities and people involved. The positive results can be shared with the international IEM community that will see the UMD as an example of a way to progress the field. Not only will we make many new diagnoses, discover new diseases and elucidate pathogenesis, but we will also implement new technologies into clinical practice. Altogether, these results can be made visible to the scientific community in many ways accelerating scientific progress in the international field.

Work package 4. Innovative treatment and outcome

Work package coordinators: Dr Hidde Huidekoper (Erasmus MC) & Dr. Pim Pijnappel (Erasmus MC)

Overall aim of work package

One of the aims is bringing together the different platforms of the national metabolic centers on the development and implementation of innovative therapi*es (translational research).* Translational research implies the collaborative efforts of clinicians and basic scientists of bringing treatments from the laboratory (bench) to the patients (bedside). We aim to support the development of new therapies “From idea to reality” with a clear focus on the patients that may benefit from the therapy. It should be stressed that for many inherited metabolic disorders such therapies may present relatively easy, straightforward and inexpensive interventions making use of available medications and/or diet adaptations. This will follow from the elucidation of the underlying pathophysiology of the diseases (WP3).
A second aim focusses on the evaluation of the clinical effects of both innovative and existing therapies for patients: the choice of clinical outcome parameters is of crucial importance to capture the effect of treatment. Finally, this work package aims to support clinical trial design by bringing together national knowledge and expertise on conduct of clinical trials, optimal clinical trial design, clinical outcome parameters, patient reported outcome, collection of patient data and materials and development of new functional clinical tests, clinical trial databases and interpretation of clinical study results.

Specific objectives

1.1 Inventory of national expertise and platforms for the development of innovative treatments
1.2 Support development of innovative treatments
1.3 Assessment of patient outcome of metabolic diseases in the Dutch newborn screening program (both current diseases and diseases to be added to the program in the upcoming years).
1.4 Assessment of patient outcome of metabolic diseases with different treatment strategies.
1.5 Inventory of national expertise and infrastructure for conducting clinical trials for metabolic patients
1.6 Initiating / catalyzing clinical trials for innovative treatments, nutripharma-based interventions or repurposing of existing drugs.

Work plan in brief (including provisional time line)

1.1 A national inventory will be made on current clinical research activities and expertise in the different UMCs. This inventory will promote dissemination of ongoing clinical research activities and patient participation in these activities. Requires input and participation of clinicians, laboratory experts, researchers and coordinator.
1.2 Installation of "think tanks" composed of clinical and laboratory researchers from different centers to provide advice and input for innovative treatments, including stem cell research, gene therapy, tissue targeting and nutripharmaca. Requires input and participation of clinicians, laboratory experts, researchers and coordinator.
1.3 Defining standardized follow-up protocols and implementing these at all metabolic centers is necessary to collect and analyze uniform data on the efficacy of the Dutch newborn screening program. As new metabolic diseases will be added to this program in the upcoming years, it is essential to define the parameters on which the clinical efficacy for each metabolic disease in the newborn screening program should be evaluated before initiation of screening. This should also be done for selected metabolic diseases in the current newborn screening program for which the benefit of screening has not been fully established (e.g. OCTN2 deficiency, 3-MCC deficiency). In collaboration with WP1 an infrastructure (database) will be set up in order to collect all data. These databases can then be used as core databases for projects aimed at studying the clinical outcome in specific metabolic diseases included, or to be included, in the Dutch newborn screening program. Requires input and participation of clinicians, laboratory experts, researchers and coordinator.
1.4 For some metabolic disorders different treatment options are available, but comparative data on treatment outcomes are lacking. Clinical data on patient outcome from centers using different treatment strategies will be brought together and analyzed, also in collaboration with other international centers (i.e. in collaboration with the MetabERN, the European Reference Network for metabolic diseases). This includes defining protocols for standardized follow-up, including standardized evaluation of cognitive outcome in metabolic diseases affecting the central nervous system. Requires input and participation of clinicians, laboratory experts, researchers and coordinator.
1.5 A national inventory will be made of each center’s infrastructure for conducting clinical research. Based on this inventory an UMD clinical trial network will be constructed based on smaller subnetworks/working units of the different disciplines (e.g. epidemiologists, data managers, statisticians, research nurses etc.). These working units can be used as ‘think tanks’ to tackle questions and problems related to designing and conducting clinical trials (see also 1.6). Requires input and participation of clinicians, laboratory experts, researchers and coordinator.
1.6 Selected novel therapies developed at the preclinical level will be translated into clinical trials. Clinical trials may also include repurposing of existing drugs or novel dietary interventions for different metabolic diseases. Depending on the available budget, these trials will be supported by the UMD catalyst grants . Support will include help to arrange specific regulatory affairs e.g. related to the testing of stem cell- and/or gene therapy-based approaches. Requires input and participation of clinicians, laboratory experts, researchers and coordinator.

Challenges and Mitigation Strategy

- The development of novel treatment options will be time consuming and requires extensive investment of personnel and finances, and it has a high risk factor. Nevertheless, it is the ultimate goal of the UMD to promote and develop successful treatment options for inherited metabolic disorders. Combing efforts in the UMD

provides opportunities and challenges. Opportunities include the possibility to learn from each other and to compare different approaches and systems, which can help improving other efforts. The challenge is how to invest the available funding in a sensible manner. Given the complexity of these objectives and the highly ambitious aims, combined with the relatively limited funding, we aim to strengthen existing efforts and projects in this area rather than starting new projects. Funding should be sought from other sources than via UMD as well, and international collaboration will be essential.

- It will be challenging to assure the collection of complete data as defined in the minimal data sets for inherited metabolic diseases included, or to be included, in the Dutch newborn screening program, as well as for other metabolic diseases and future collaborative projects within UMD, as resources (time and funds) are limited. In order to monitor that data are collected according to the defined minimal data sets and entered in the database designated time for staff should be made available at each center.

Impact for field of inborn errors of metabolism, UMD, science and society

The impact of the development of novel therapies for metabolic disorders will be very high, both in NL and globally, as there is a high need to develop treatment options. Construction of the UMD clinical trial network will catalyze the development of investigator initiated clinical trials and will improve the design and effective execution of these trials, thereby improving the prospects for patients with metabolic diseases in general. Conducting clinical outcome research either on the efficacy of implementation of newborn screening for specific metabolic diseases, comparing different treatment strategies for certain metabolic diseases or assessing cognitive outcome in metabolic diseases affecting the central nervous system will expand our knowledge on these diseases, will identify knowledge gaps and will identify possible new targets for (therapeutic) interventions.

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Work package 5. Administration and governance

Work package coordinators: Dr. Clara van Karnebeek (Amsterdam UMC) & Prof. dr. Hans Waterham (Amsterdam UMC)

Overall aim of work package

This work package combines all management and organizational requirements and efforts to establish, manage and expand the UMD in a sustainable collaboration.

Specific objectives

1.1 Overall management of UMD
1.2 Development of external communication tools and strategy for UMD, including logo and website
1.3 Development of governance model for UMD
1.4 Establish UMD as legal entity and arrange collaboration intention agreement between participating UMCs
1.5 Responsible for overall UMD program development and associated budget outline
1.6 Consultation with external organizations and stakeholders, including Metakids, patient organizations, ZonMW, NWO, UMC boards, No 5 foundation, Media etc.
1.7 Constitute a “Nationale Wetenschapsagenda” for inherited metabolic disorders with stakeholders, including clinicians, scientists and patient organisations
1.8 Identify different funding and collaborative opportunities to sustain and expand the UMD

Work plan in brief (including provisional time line)

1.1 WP5 includes the tasks of the two program directors, who are responsible for overall development and management of the UMD program. Includes organizing on line and in person meetings with WP coordinators and contacts with stake holders.
1.2 Important priority is to develop a recognizable logo for UMD. Website domain already claimed and initial website installed. Needs to be further developed, including public domain and UMD participants domain. Requires IT input and input of UMD participants, project manager.
1.3 Directors will come up with proposal for governance and will consult WP leaders and selected stakeholders/advisors for input and feedback.
1.4 As advised per UMC board of the Amsterdam UMC, the UMD will be registered as a legal foundation, which can then negotiate a collaboration intention agreement between the UMD, the different UMCs and the NFU
1.5 A plan of action for the first 5 years will be established with the input of the WP coordinators, including an associated budget proposal which will then be negotiated with Metakids.
1.6 The program directors will be responsible for the contacts and consultations with other organizations and stake holders interesting for the goals of the UMD and/or interested to collaborate with the UMD

1.7 A “Nationale Wetenschapsagenda” will be drafted with input from all stakeholders, coordinated by the program directors and operating committee, which describes scientific, clinical and societal challenges and shortcomings and is used by the Dutch government as a guide for future policy and funding

1.8 Create and manage a short and longterm plan for obtaining funds from different sources (pivate, public, governmental) and forging collaborations nationally and internationally.

Challenges and Mitigation Strategy

- Development and management of a consortium as complex as the UMD is very demanding with respect to required input of time and effort and so far has been done in addition to already demanding jobs of both directors (and without compensation). This includes arranging meetings, instructing colleagues, handling the finances and HR, writing letters, reports, emails etc etc, which are tasks that should be handled by a project coordinator to allow the directors to focus on issues that cannot be handled by a coordinator. In addition, albeit to a lesser extent, the same is true for the work package coordinators.
- More funds are needed to guarantee UMD sustainability and success; in the current competitive climate chance of success of funding applications is suboptimal. However, through collaboration and early successes, we aim to independently apply for funding (ZonMW, EU, RvBs, NFU etc) and work with Metakids and other partners to raise the moneys required.
- Effective and transparent governance is a challenge; we have developed an innovative model to achieve this based on other consortia and joint experiences.