ESF/EMRC Exploratory Workshop

"Rare Metabolic Diseases in Adulthood"

University Medical Center (UMC), Utrecht, 3-6 May 2001

Final Report

FINAL PROGRAMME:

Thursday:		14:00	Introduction and general outline of the meeting, dr H.W. de Valk
		14:30	Introduction ESF, dr M. Minkowski
		15:15-16:30	# Explanation and questions about TEAM-study approach # Exploratory meeting approach Examples of possible initiatives TEAM-study II # Possibilities for grant applications
Friday:	Morning:	9:00-9:30	Explanation groups and work
		9:30-11:30	General exploratory discussion
		11:30-12:30	Discussion in separate groups
	Afternoon	13:30-15:00	Discussion in separate groups
		15:00-16:00	Plenary session
		17:00-21:00	Social Programme + Dinner Boat "Domstad"
Saturday:	Morning	09:00-12:00	Feedback and plenary discussion Analysis and suggestions: Dr P.J. Lee Prof. C. Scriver Dr A. Boneh Prof. J.M. Saudubray
	Afternoon	13:00-15:00	Integrated summing-up Practicalities, conclusions and planning
Sunday:	Departures		

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SCIENTIFIC CONTENT OF THE EVENT:

Title of the Exploratory Meeting:
ESF-exploratory Meeting on Rare Metabolic Diseases in Adults

Participants: 20

Objective of the meeting:
The aim of this exploratory meeting is to bring together experts in the field of rare metabolic diseases to plan collaborative activities which should result in separate research working groups dealing with a number of diseases and common clinical problems. Since the diseases have myriad pathophysiologic bases and complications, scientists from different disciplines are invited.
These experts will attend a three-day discussion meeting to explore the current research questions and to plan collaborative actions, both in design and financial dimensions. The topics will be discussed in small groups followed by a plenary discussion.
The results of the plenary sessions will be formally approved by the participants and form the basis of future actions

Thursday 3 May 2001

After a word of welcome, the aims and objectives of the meeting are set out again.
Dr Minkowski briefly describes the history, nature and policies of the European Science Foundation as well as the funding possibilities and policies.

-Exploratory meetings
-Creating Networks
-Euro-core program

The discussion then focuses on the already started TEAM-study (Transfer of Expertise on rAre Metabolic diseases in adults) in which some of the participants already participate. The general aims and objectives, process-mechanisms and proposed end results (deliverables) are described.
(see slides)

In the discussion that follows, a number of items are brought up and discussed:

-Involvement of a publishing agency
-Involvement of a recognized journal; possible publication of the end results as a “special issue”
-Or producing a sort of textbook for education purposes?
-Review of quality of publications: 2 different readers as discussed
-Contacting local technology systems for supporting the project

After this discussion, the possibilities for grant application in the European Union and related and unrelated European institutions are briefly presented.
(see slides)

Finally, the working program for the next day is discussed.

Friday 4 May 2001

The days starts with a group discussion on the way forward and the scope of the meeting. A number of items and suggestions are discussed which will be described:

The idea is put forward to generate a kind of “European network” of individual professionals, groups of professionals and institutions interested in the field of rare inborn errors of metabolism. This collective can be the basis for national groups to initiate research and for international collaborative groups to start an international project.

The German group of Wendel et al. is present and their current grant application in Germany may contain templates of protocols which can be used in collaborative studies.

To prevent double work, contact and communication with national registries is important.

The ESF is an institution, which may be approached for funding. Funding includes the planning and building of such a network by facilitating meetings and by facilitating the creation of an Internet-site (website). Such a collective requires a Steering Committee, which may also be funded by the ESF.

It is understood that such a network is European in origin and scope but will have global links and interconnection. Such a collaboration supports groups on other continents in efforts to obtain funding. Vice versa, intercontinental collaborations supports European groups on an national level. Similarly, European collaboration in itself may help national groups to get funding from national agencies.

The discussion focuses on the nature and scope of such a core network. It is finally agreed that the main theme will be "Rare inborn errors of metabolism in adults".
To assess whether such a network would really be viable, PKU can be used as a starting point. With a positive experience, other subjects and diseases will follow.

Such a network can also be used to help in performing clinical trials by allowing recruitment of sufficient numbers of eligible patients and by convincing agencies and industries to support these trials. An example can be the PAL-project (phenylalaninelyase) as described by Scriver. PAL is taken by mouth and lowers plasma phenylalanine levels by degrading phenylalanine in the intestines, both phenylalanine from food and from the body pool.

A number of initial prerequisites are discussed:
-definition of disease and essentials diagnostic criteria
-data to be obtained from patient files must be concise and easily providable by participating centers and individuals.

After this lengthy discussion, the participants retreat in 4 topic groups, all related to PKU which will be the initial disease to be covered as will serve as template and guinea pig:

PKU in pregnancy group

(Lee, Naughten, Schwarz, de Valk)

Comments after pregnancy presentation:
-There is a definite risk of small baby by over-restrictive nutrition with too low plasma phenylalanine levels.
-There is a definite need for a meta-analysis to try to establish "safe" levels in different periods during pregnancy.
The suggestions:
-To do an easy survey to assess the size of the problem: women at risk and the knowledge about procreation issues.
-Study nutritional issues
-Role of the genotype of the fetus on pregnancy outcome
-Meta-analysis on target levels
-A prospective study: clinical trial on the value of tyrosine supplementation during pregnancy

Bone disease in PKU:

(Boneh, Sääf, Parrot-Rouland, Barrientos)

Discussed items
-survey of patients with symptomatic and asymptomatic osteoporosis
-study of different groups: early and late diagnosed patients, on diet or off-diet, well-controlled or poorly-controlled
-pregnant women are a special group: what happens to the Mineral Bone Density during pregnancy: with well- and poorly controlled diet and during lactating
-assessment: height and weight, dexa-scan, bone biopsy, vitamin k status, nutritional adequacy, renal function, bone markers, anabolic markers

Comments after osteoporosis presentation:
-for the assessment of the nutritional adequacy we need a standardized protocol
-vit D status is difficult to measure
-how about exercise
-is an abnormal finding due to misuse of the skeleton or due to the diet??
-CT optimal method to measure bone density?

Neurophysiological and neuropsychological issues
(Kuhl, Burchard, Wendel, de Koning, A. Burlina)
Discussed items

Comments after presentation
-a standardized method of looking at the data is needed
-definition of poor metabolic control?
-sibs as a control group
-obvious need for a clear research question
-controlgroup are the sibs?
-what can be such a research question
-training of the researcher to do the same neurological test

New treatments and approaches in PKU
(Scriver, Burlina, Dorland, Fekete)

Saturday 5 May 2001

This day starts with a plenary sessions, recapitulating the results of the previous day. Saudubray has now joined the group.
The discussion reverts back from yesterday's disease-related topics to the general theme of the website. It is decided to take PKU as an example to test the workings of the collective and the website. It is discussed that each country has a considerable number of PKU-patients. The policy regarding the age at which to stop the diet differs among countries and this difference provides a fine tool to assess the effect of these different policies on crude outcome.
This idea needs a simple recruitment policy and a simple assessment mechanism. The 7-questions-list by Tracey et al. will provide such an assessment as will the assessment form used in the Glycogen Storage Disease study. See Appendix B. These questions will, be easy to answer by the treating physician and will center upon life/death, schooling, professional occupation (socio-economic issues) and other events (such as marital status and procreation). The information form this assessment will describe is the effects of the efforts of pediatricians and will help them to optimize treatment and care.

After the successful building of the web and the successful first initiative, other diseases will be dealt with. These diseases will come from a list drawn up by Saudubray. This list is also used to show future participants from the first moment onwards what the scope and the objective of our initiative is. These participants can be recruited from different professional disciplines.
Recruitment and acceptance of contributing physicians will be dealt with by the national representative or professional body and/or the Steering Committee.

The title of the network is:

NIMDA
Network of inborn (or intermediary) metabolic diseases in adulthood

The European definition on being an adult is an age of ≥ 18 years.
The European definition of a rare disease is: prevalence ≤ 5/10.000 inhabitants

Mission statement of NIMDA

To establish a functional network to aid the study of the natural history of inborn metabolic disorders in adulthood by and through diagnosis and treatment to improve care and outcome.

Some other items are then discussed:
-who will be the webmaster?
-collective ownership
-no access possibility for patients or patient organizations
-confidentiality and privacy issues
-ad ONIM-number to diseases
-organizational structure: each country has a representative; according to the guidelines of the ESF the Steering Committee can have a maximum of 12 members. The composition and activities of the Steering Committee will be dealt with at a later stage.
-other continents can provide visitors/experts to the Steering Committee and d/or provide corresponding members
-admittance of new members after the start of NIMDA has to follow certain rules
-linkage to other databases
-some logistic problems are discussed:
    -date of entry of the data
    -entry per patient
    -families identification by dot
    -name, date of birth, death, sex, diagnosis, center
    -how the diagnosis was established
    -free text about the verification
    -also categorizes the identification: e.g. clinical, mutational, biochemical, enzymatic; definition of levels of evidence to accept the diagnosis

The discussion then regresses to ground already covered, but finally the initially agreed approach of a central core database with PKU as a test-disease (feasibility) is re-iterated and agreed. This takes also into account the funding probabilities of such an approach by the ESF. The approach as outlined above has to be stated end explained very clearly to all potential participants in NIMDA.

Final plan of action:
-grant submission of NIMDA to ESF (see submitted grant application, deadline 31 May)
-evaluation of NIMDA by other European and national societies

CONTRIBUTION TO FUTURE DIRECTION OF THE FIELD:
Grant application for the ESF-network programme

NIMDA: Network on Inborn Metabolic Disorders in Adulthood

Aim of the NIMDA-project
The aim of the "Network on Inborn Metabolic Disorders in Adulthood" (NIMDA) is to establish a functional network to aid the study of the natural history of rare inborn errors of metabolism in adulthood with assessment of the benefits and side-effects of treatment in order to improve care and outcome.

Abstract
The aim of the NIMDA-project is to establish an Internet-based electronic network to serve the professional community involved in rare inborn errors of metabolism in adult patients. NIMDA will provide an electronic home and meeting place for professionals from different disciplines who are involved in the care for these patients and in the research on these diseases. This meeting place will result in improved communication and will also result in the generation of new research as well as educational initiatives. Adult patients with rare inborn errors of metabolism are a newly emerging and growing group. Through the vast improvement in obstetric, neonatal and paediatric care, many of these individuals with hitherto disease which were fatal or led to a life in an institution, are now able to function in the open society. These individuals however require lifelong care, counseling and support. The low frequency of occurrence of the individual diseases, the limited experience and the limited availability and accessibility of good information create a difficult situation leading to non-optimal diagnostic and therapeutic strategies at great costs for the patients and the community. NIMDA aims at attacking this problem by providing a framework for interaction between professionals. In this framework, new initiatives on educational, care and research will be born by bringing together professionals from different countries and facilitating communication. NIMDA also aims at establishing a meaningful discussion site between professionals and governmental agencies, non-governmental agencies and industry, in collaboration with patient groups. In this way, patient participation in the medical process will be strengthened, development and testing of drugs can be facilitated and the foundation of general health care policies will be improved.
NIMDA will take full advantage of the European scope and possibilities and will result in a electronic center focussed on all involved in the care of adults with rare inborn errors of metabolism.

Background of the proposal
With the improvement in obstetric, neonatal and pediatric care, the outlook for children with rare inborn errors of metabolism has greatly improved. Currently, many patients with these diseases reach adulthood in such a good condition that they are able to participate in society in contrast to some years ago when many would die early in life or end in an institution. However, optimal participation of these individuals requires special and life-long care and support. The number of diseases which can be treated adequately are growing with improving care leading to a steadily increasing number of adult patients. These beneficial changes have created new problems and new expertise requirements. These problems and requirements regard issues as the necessity of continued treatment, the occurrence and treatment of acute and chronic organ complications, pregnancy and childbirth, risk of disease in progenity, long-term prognosis and signs and symptoms in family-members who are heterozygote for the disease.
These "new" patients with rare metabolic diseases and their families need comprehensive and integrated care from adult physicians, calling for specific expertise in the field. Often therapy includes dietary modifications and restrictions with food supplements and oral medication, all of which have an important impact on the quality-of-life of patients (adults as well as children) with these diseases. At the same time, there is not much experience with these new patients and the limited expertise is scattered and not readily accessible. There is an urgent need to expand the knowledge and expertise based on pooling and analysis of data on these patients, and based on observational and intervention studies. Careful analysis of adult outcome of pediatric care for example will help optimize pediatric

care and will be a powerful tool in elucidating the natural history of the diseases in adulthood and the benefits and side-effects of treatment. It will help to answer the questions related to length and type of dietary and pharmacological treatment, thereby helping in deciding treatment policy during childhood and adulthood. It will additionally create a sound basis for counseling of patients and families and will also help to formulate general policies. Since these diseases are individually rare, such studies need an international collaborative effort.

The need for a Network

Since the frequency of the various diseases is low and the expertise on these diseases is scattered and not readily accessible, intensive international collaboration is mandatory to allow progress in this field. This means building a Network. The European scope would certainly provide a framework for such a collaborative effort. In such a network, professionals from different disciplines involved in the care of patients and research in these diseases are brought together and such a network offers a continuous interactive mechanism leading to the generation of different working groups on different diseases and complications. By combining the information from medical centers from a number of countries with, at times, different strategies in patient groups, the European scope will also offer insights into the importance of geographical factors, cultural factors and aspects of treatment strategy. The scope of these working groups can be manifold, including pathogenetic studies, observational studies, intervention studies as well as educational programmes. Facilitating pharmaceutical studies will clearly help to improve and speed up the treatment with orphan drugs. This network will be Internet-based to provide easy accessibility and good communicability while any issues about patient confidentiality are taken into account. The network will be owned by all participants but will be coordinated by one center.

The proposed NIMDA-network activities in a period of three years:

The activities

1: *The initial establishment of the web-based home of NIMDA*

NIMDA will have a site on the Internet. This website will be coordinated by a webmaster. The webmaster will also coordinate, in close collaboration with the participants, the contents and layout of the site to optimize usability. A list of diseases to be covered ultimately by NIMDA will be drawn up by the Coordinating Committee. This list will be based on an analysis of diseases which will be encountered in adults which will be published shortly by prof. Saudubray (Hôpital Necker, Paris, France). This list will contain a number of diseases of carbohydrate, lipid, protein or nucleic acid metabolism. The site will be targeted at professionals and their organizations with links to patient organizations, to other relevant institutions and to industry.

Deliverables of the NIMDA-network after three years

NIMDA will provide to the European professional community a means of rapid communication, which will be

1: allowing the formation of working groups aimed at research on rare diseases in adults
2: facilitating communication between professionals of various disciplines on rare metabolic diseases in adulthood
3: providing a framework allowing clinical trials including those on orphan drugs
4: establishing educational services and facilities for the various European countries
5: providing the possibility of forming groups supporting communication between professionals, patient organizations, governmental agencies and industry.
6: communication with governmental agencies, patient groups and industry

2: *Testing the viability and feasibility of NIMDA by assessing aspects of a particular disease: phenylketonuria (PKU)*

The NIMDA-concept has to be tested. We propose to do that by way of assessing key-elements of a classic, well-known disease: Phenylketonuria (PKU). PKU is a suitable test-disease because it is relatively frequent (1/10.000-18.000 newborns/year), it is treatable and the outlook with treatment is good. As a test of NIMDA, a simple questionnaire of key

questions regarding treatment outcome and psychosocial items will be sent to participating centers. The questionnaire will be based on the one used by Treacy et al. (Am J Hum Genet 1995; 56: 359-367). The questionnaire deals with an elementary evaluation of treatment outcome, reproductive capability, somatic and intellectual development and on social adaptation and capability (learning impairment, work impairment, cosmetic impairment). This PKU-test will not only test the NIMDA-concept but also information will be gathered on the outcome of this disease and feedback will be given to the pediatric-metabolic physicians on the effects of their efforts on outcome in adulthood. This PKU-test is only a template for other diseases as mentioned earlier.

3: *Expanding NIMDA*
After the successful establishment of NIMDA as an electronic center for participating professionals and after proof of workability with the PKU-test is obtained, the scope of NIMDA will be widened to include the other diseases from the list outlined above. NIMDA will act as a initiation nucleus for new initiatives and will actively support these initiatives (grant applications, electronic and logistic support).

The proposed activities will thus cover the establishment and testing of the NIMDA-network together with providing in the last stage the groundwork for the expansion of NIMDA to include the identified diseases. This NIMDA-network provides an electronic home and meeting place for European scientists and health care professionals allowing new initiatives which can only be done in this way to produce reliable and relevant information because of the relative low frequencies of the individual diseases and the lack of reliable and readily accessible knowledge. It is envisaged that after three years, there will be a functioning network which will apply for other grants from national, international and European sources. The Eurocores programme for example may be a possibility. Also, financial resources can be generated from own activities of NIMDA like educational initiatives and working groups can separately apply for grants and perform profitable activities within the limits of their chosen subject matter.

The organisation and administration
Participants
Participants are individual professionals representing institutions in the field of rare metabolic diseases. These professionals are essentially from Europe while linking up with key professionals from other continents (like the USA, Japan and Australia for example). The initial participants will be the founding members (see Appendix).The participants will be independent members of NIMDA and may choose to collaborate on, or to exclude themselves from any individual program. They can suggest and perform their own studies as well. The participants will collectively own the NIMDA-concept and the NIMDA-website. There is no definite maximum of participating centers.
A major issue is the eligibility of new participants to join NIMDA. Professionals can be proposed by the representative of the country in question with the ultimate decision on admittance of a professional resting with the Coordinating Committee. Professionals wanting to join NIMDA should be a member of a national scientific society and/or the Society for the Study of Inborn Errors of Metabolism. In this way, unwanted information and information of doubtful quality can be barred.
Finally, because sometimes patient data may be involved, a rigid policy on patient anonimity will be put in place using existing schemes from established databases as example.

Management
There will be a central Coordinating Committee, composed of up to 12 representatives of the founding members (see Appendix). There will be a scheme of rotation of these representatives between countries and blocks of countries, providing continuity and sense of direction. The Coordinating Committee will also have a final decision on admittance of new members. The aim of this mechanism is to safeguard the reliability and integrity of NIMDA with continuous good quality of initiatives.

Coordinating center
The department of Internal Medicine of the University Medical Center, Utrecht, The Netherlands will perform the task of Coordinating Center on behalf of the collective of participants

Definition of subject matter
NIMDA will deal with adults (age ≥18 years) with rare metabolic diseases (prevalence ≤ 5/10.000 inhabitants).

Setting and context of NIMDA
NIMDA is an initiative in a new problem area. There are a number of national databases providing logistic information (professionals and institutions) and limited information on the diseases for professionals and patients. NIMDA will have conceptual links with these databases but will have a much broader scope and content. Education is currently a major topic in the EU-project: "*T*ransfer of *e*xpertise on r*a*re *m*etabolic disease in adults" (TEAM). This TEAM-study is in the process of designing and performing key-courses on this subject matter, after quality-assessment of expertise and establishing a consensus approach to cope with specific challenges in patient care.

Working plan and time schedule of the development of NIMDA
First phase of NIMDA
A first concept and layout of the NIMDA-site will be designed by the Coordinating Center with consultation of the founding members and will be put on the Internet after approval by the Coordinating Committee. A webmaster will be involved in the designing, layout and building the website as well as the maintenance and operation of the website. The time required is estimated at 18 months.

Second phase of NIMDA
The NIMDA-concept will be tested by a trial run using PKU. Participants will be asked to answer a number of elementary questions on their adult patients with PKU. An electronic form on the NIMDA-website will be used to this purpose. The data will be centrally collected and processed by the coordinating center. Statistical analysis will follow with generation of a report. This will be done by the coordinating center and will be produced in collaboration with the participants. The final report will be published after approval by the Coordinating Committee. The time required is estimated at 12 months.

Third Phase of NIMDA
The third and last phase of NIMDA will deal with the enlargement of the scope of NIMDA with inclusion of more diseases. The basic structure for the integration of these diseases providing a core of essential information technology utilities will be established. The time required is estimated at 6 months.

Diffusion and dissemination

NIMDA will form an electronic home and meeting place. By providing such a place, new initiatives will be created and subsequently carried out by working groups. The results of these efforts of the working groups will be published on the site and will be distributed through other electronic (CD rom) and non-electronic means (hard copy material). Educational activities will result in teaching courses and teaching material. Teaching material will also be made available through electronic and on-electronic means. The website of NIMDA will allow visits by all kind of professionals and links will be provided to other databases and relevant sites. Although NIMDA is a network meant for professionals, close collaboration with patient groups will provide an integrated approach.

NIMDA Network Budget

	EURO's
First year	
Information technology costs	
-Building the website	25.000
-Maintenance of the website	1.500
Costs coordinating center	
-Logistical support (material)	2.000
-Logistical support (office management):	10.000
Coordinating Committee	
-Travel costs and subsistence meetings	
(two annual meetings, 6 persons, 2 days)	12.000
Second year	
Information technology costs	
-Maintenance of the website	1.500
Costs coordinating center	
-Logistical support (material)	2.000
-Logistical support (office management):	10.000
Coordinating Committee	
-Travel costs and subsistence meetings	
(two annual meetings, 6 persons, 2 days)	12.000
Third year	
Information technology costs	
-Maintenance of the website	1.500
Costs coordinating center	
-Logistical support (material)	2.000
-Logistical support (office management):	10.000
Coordinating Committee	
-Travel costs and subsistence meetings	
(two annual meetings, 6 persons, 2 days)	12.000
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Total projected expenses:	101.500

APPENDIX

NIMDA Network Participants

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