Transfer of expertise in adults with rare metabolic diseases

(TEAM-study)

Final report
2000-2002

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1: General information

Name of the project
Transfer of ***E***xpertise in ***A***dults with rare ***M***etabolic diseases (TEAM)

Funding of the project
Funded by the European Union in the action programme "Community action on rare diseases";
Code: RD 2000/10008.

Period of the project
Dec. 15, 2000 – Dec. 14, 2002.

Project team

H.W. de Valk	project-leader
Z.M. Barrientos	project-associate
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2: Summary

General aim of the project

The aim of the project is to improve the quality and dissemination of expert knowledge on an emerging group of patients: adults with rare metabolic diseases. Patients with these diseases hitherto often did not live to see adulthood in a reasonable condition, if at all. Expertise on this subject is limited and scattered among a few experts in the field.

This improvement is thought to occur through quality assessment of current expertise followed by presentation of the results in an accessible form on the Internet, a hard copy presentation and a set of training sessions. This means that there are four main ultimate products: A: Quality assessed body of knowledge; B: Internet site; C: Hard copy presentation; D: Training session.

There are 8 main operational parts in the project:

(1): Formation of expert groups
(2): Determination of relevant source material of sufficient quality
(3): Quality assessment of current literature
(4): Establishing the reviews for the dissemination process
(5): Launch of the Internet site
(6): Design of the hard copy
(7): Design of the training session
(8): Performance of the training session with presentation of the hard copy book.

Management

The contract period ran from December 15, 2000 to December 15, 2002. Operational management was done by the Co-ordinating Centre. Decisions were taken by the collective group of participants present at the meetings. Decisions were translated into practical policy by the Co-ordinating Centre.

Theoretical structure of the project

Source material

The review work is done by expert groups. They select relevant titles on the basis of literature searches done in databases by the Co-ordinating Centre. Abstracts from the selected titles are provided and the groups select the relevant abstracts. The papers from which these abstracts stem are provided to the groups as working materials. These working materials are subsequently used for analysis and writing of a review test. This review constitutes endproduct A (operational part 1-4), although it is a fluent and changeable product.

Dissemination

Dissemination first uses the Internet site, managed by the Co-ordinating Centre (UMC, Utrecht, The Netherlands); this is endproduct B. Second, the hard copy format is established and the hard copy produced by using the reviews of endproduct A; this is endproduct C. Thirdly, the design of the training session is made, filled with the endproduct A and performed; this is endproduct D.

Practical performance and adaptation of the project

Source material

In the two years of the project, 7 meetings have been held with partners in this project to initiate, monitor and adapt the process. During the first months of the first year, the six groups were formed, headed by an expert in the field as had been agreed in the design of the project. Each group had a distinct set of topics. These groups were to operate autonomously. The structure of the project as agreed started with the analysis of literature with identification of the sources of sufficient quality. At that point, a number of stumbling blocks occurred that necessitated adaptation of the project design and has delayed the development of the project. These stumbling blocks are:

Geographical spreading of members of a working group may be desirable from the prospect of Europe-wide initiatives, it severely slowed down the process. This meant that during the first year of the project, groups had to be rearranged. This also took time.

One group did not perform their task at all. This meant that the subjects and topics of this group has to be re-allocated and in the end the Co-ordinating Centre took on the major task of this group which means a long delay.

The autonomy of the groups was in practice too great for adequate functioning of the groups, reinforced by the fact that because it is a new field and because there is a limited number of experts, the members of the groups have an overloaded programme already and the credits are uncertain in this experiment. This means that currently the Co-ordinating Centre has a directive role in all the groups to ensure the optimal outcome.

The above-mentioned development have meant that there was a considerable delay in the course of the project and has also led to the investment by the Co-ordinating Centre of human and financial resources after the formal end of the contract period to allow the completion of the review process and the performance of the dissemination activities.

Dissemination

The three dissemination actions have been prepared. The Internet site for the TEAM-I project is available from December 1, 2003 with subsequent filling of the review spaces (endproduct B). The design of the hard copy has been agreed upon during the final contract-meeting on February 7-9, 2003 (endproduct C). The training sessions has been designed and agreed upon during the same meeting (Endproduct D). Due to the review delays, these three activities had to be postponed during the course of the project. The Internet site is launched but will be filled in the period January 1, 2004-July 1, 2004.The training sessions with presentation will be held for the first time form August 28-30, 2004, in connection with the meeting of the Society for the Study of Inborn Errors of Metabolism.

Presentations

The project leader has performed a number of activities to promote the TEAM-approach and products in general of the activities in this new patient group. There have been 15 activities, detailed in the General Report.

Outlook and perspective

There project now end the review stage and the dissemination structure for the use of the reviews is in place. This means that the aims of the project will be achieved in 2004. Thus, the objectives are achieved, but later then it was originally planned and agreed. The experience with such a project in a new field and in a network of collaborating partners throughout Europe has provided experiences that are used in the conduct and adaptation of the TEAM-2 project. By using these experiences in the TEAM-2 project, it will be possible to perform that project in accordance with the original design and within the time-framework of the contract of TEAM-2.
A number of links has been established with other websites that can be found by visiting our site. The TEAM-1 products (hard copy and training session) will be available after the first performance.

Conclusion

The TEAM-1 project has met with difficulties in the first stage of the project (the reviewing stage) that required adaptation of the design of the project and considerably delayed the course of this stage. The second stage (the dissemination process) has been designed and is organised and can start with the completion of the review materials. The Internet site is launched; the hard copy will be presented at the first training session that will be held in August 2004.

3: General report

3.1: Goals of the EU-funded project:

"Transfer of expertise in adults with rare metabolic diseases" (TEAM-1).

The goal of the project is to improve the quality and dissemination of expert knowledge on an emerging group of patients: adults with rare metabolic diseases. Patients with these diseases hitherto often did not live to see adulthood in a reasonable condition, if at all. Expertise on this subject is limited and scattered among a few experts in the field. Items related to diagnosis, treatment, complications, pregnancy and prognosis will be covered. This improvement is thought to occur through quality assessment of current expertise followed by presentation of the results in an accessible form on the Internet, a hard copy presentation and a set of training sessions. The set of reviews leads to a composite set of reviews that can be used as a changing source of knowledge.
The main target audience for the dissemination activities are European medical professionals or those being educated to become one. The design and target audience means that there are in-depth reviews as distinct form a mere description of the disease. Diagnosis and treatment issues, even if there is no or little reliable information around, will be discussed. However, directive guidelines are not meant to be a product of the project.

3.2: Design and course of the project

In the project, there are two stages of development:
I: Review process using quality assessment of expertise
II: Dissemination of the reviews

Based on these two stages, there are four main ultimate products:
Review process:
A: Quality assessed body of knowledge, resulting in a set of reviews

Dissemination:
B: Internet site
C: Hard copy presentation
D: Training session.

To achieve these 4 ultimate products in these two stages, eight operational parts were designed:

Review process:
(1): Formation of expert groups
(2): Determination of relevant source material of sufficient quality
(3): Quality assessment of current literature
(4): Establishing the reviews for the dissemination process

Dissemination:
(5): Launch of the Internet site
(6): Design of the hard copy
(7): Design of the training session
(8): Performance of the training session with presentation of the hard copy book.

Management
The formal contract period ran from December 15, 2000 to December 15, 2002. was done by the Co-ordinating Centre. Decisions were taken by the collective group of participants present at the meetings. Decisions were translated into practical policy by the Co-ordinating Centre.

3.2.1: Review process

In the two years of the project, 7 meetings have been held with partners in this project to initiate, monitor and adapt the process. The different meetings are listed in Appendix A and the notes of the different meetings are presented in the Appendices B-H. The sequential operational parts will be described and discussed.

(1): Formation of expert groups

During the first ("kick-off" meeting), held in Utrecht, the Netherlands from February 15-18, 2000, the six different groups were formed as agreed with the partners beforehand. The lists with the six groups, the members and the topics are listed in Appendix I. These six groups were each headed by an expert in the field. These groups were to operate autonomously.

After a successful start, during the first year a number of unexpected stumbling blocks appeared in this operational part of the project.

Geographical spreading of members of a working group may be desirable from the prospect of Europe-wide initiatives, it severely slowed down the process. This meant that during the first year of the project, groups had to be rearranged. This also took time.

One group (the French group, formally headed by prof. Saudubray) did not perform their task at all. The same applies to a lesser degree to the British group, formally headed by prof. Leonard). This meant that the subjects and topics of this group has to be re-allocated and in the end the Co-ordinating Centre took on the major task of this group which means a long delay. The other groups did function reasonably well.

The autonomy of the groups was in practice too great for adequate functioning of the groups, reinforced by the fact that because it is a new field and because there is a limited number of experts, the members of the groups have an overloaded programme already and the credits are uncertain in this experiment. This means that currently the Co-ordinating Centre has a directive role in all the groups to ensure the optimal outcome.

The above-mentioned development have meant that there was a considerable delay in the course of the project and has also led to the investment by the Co-ordinating Centre of human and financial resources after the formal end of the contract period to allow the completion of the review process and the performance of the dissemination activities.

(2): Determination of relevant source material of sufficient quality

To achieve this operational part of the project, research questions were formulated and relevant literature identified. The mechanisms employed consisted of a first phase of listing all title found in literature databases using key words. These searches were done by the Co-ordinating Centre. The titles were send to the groups and the groups selected on the basis of these titles the potentially relevant papers. From these papers, the abstract was send to the groups by the Co-ordinating Centre. The groups selected, after reading the abstracts, the really relevant papers. These papers were provided to them by the Co-ordinating Centre. This mechanism worked reasonably well, but was cumbersome in terms of time required. The literature searches and selection of papers was completed for the groups that worked well (Group 1,2,4 and 5). Thus, for this operational part of the project, the goal was reached within the contract period.

(3): Quality assessment of current literature

This was done by the different groups and the identification process was completed within the project period for all groups. This operational part has led to a number of draft texts. An example is shown in Appendix J.

(4): Establishing the reviews for the dissemination process

These reviews are the product of the operational parts 1,2, and 3. For reasons mentioned above, not all reviews are ready and available. At the same time we are reluctant to put these premature text on the Internet since they may be used or interpreted erroneously.

3.2.2: Dissemination process

(5): Launch of the Internet site

The Internet site is available from December 1, 2003. The formal independent address is: www.rarediseasesinadults.nl but there is an additional entry through www.umcutrecht.nl. The Internet site contains a heading TEAM-1 and this heading covers a number of pages on background, structure, topics, preliminary review texts and the agenda of the project. Visitors can respond to the site and ask questions or offer suggestions. The site contains other related items as well as general information on rare diseases and a number of links. Since contact has been made with a number of institutions, they are linked to our site. These first links currently are:

Scientific institutions	
University College London, UK	www.ucl.ac.uk
University of Padua, Italy	www.sanita.padova.it
Karolinska Institutet, Stockholm, Sweden	www.KI.se/kwh/

Professional societies	
Society for the Study of Inborn Errors of Metabolism	www.ssiem.org.uk
Nederlandse Internisten Vereniging	www.niv.nl
Societe Francais Erreurs Innate Metaboliques	
Patient societies	
Alkaptonuria Society (Liverpool UK)	www.alkaptonuria.info
Vereniging Kinderen met Stofwisselingsstoornissen	www.stofwisselingsziekten.nl
Children Living with Inherited Metabolic Diseases (CLIMB)	www.climb.org.uk
Other sites	
Orphanet	www.orphanet.com
Swedish Orphan	www.swedishorphan.com
Orphan Europe	www.orphan-europe.com
Cochrane Collaboration	www.cochrane.org
European Organisation for Rare Diseases (EURORDIS)	www.eurordis.org
North American Organisation Rare Diseases (NORD)	www.rarediseases.org

This site will be extended and updated and is ready to accommodate the texts of the reviews. The number of links will be continuously updated and the site is found when using common search machines. This site was opened later than planned because it was thought unwise and even unethical to put texts on the Internet that could be misinterpreted and not sanctioned by the participants of the project. However, detailed information on the background and other issues as well as communication details can be freely available and the site was opened after a re-evaluation of the immediate goals of the site. The site will be managed and operated by the Co-ordinating Centre.

(6): Design of the hard copy
The design of the hard copy took place during the second year of the project and was finalised at the latest meeting. The design was adapted to be able to provide a new text material to the field that was surely not already there and that was aimed at answering current clinical questions and dilemmas. The design of the hard copy book is shown in Appendix H. The hard copy book will not be entirely similar in detail as the Internet site; the Internet site will have more opportunity to adjust to remarks, questions and suggestions. The book will be printed by the company Lemma [gegevens] in the spring of 2004. The design of the book was ready at the end of the project and is ready to accommodate the text of the review process mentioned earlier.

(7): Design of the training session
The design of the training session was also decided at the meeting of the project. The design has changed during the two years of the project in order to update the design according to the newest insights in education and to optimise alignment with the current curricula in a number of academic teaching institutions in Europe. This lengthy discussion was also necessary to ensure that the training sessions were new and brought sufficient new elements to the field to make it attractive to the target audience. The design is detailed in Appendix H**.** A preliminary notification has been send to the Society for the Study of Inborn Errors of Metabolism on April 20, 2001 And a preliminary notification of our project has been send to the Dutch Society for Internal Medicine on April 22, 2001.

(8): Performance of the training session with presentation of the hard copy book.
The date of the first training session is August 28-30, 2004 in conjunction with the meeting of the Society for the Study of Inborn Errors of Metabolism. This training will be given by a number of experts in the field and provides a unique opportunity provided by the link with the SSIEM-meeting. In normal circumstances, it would not have been easy to assemble this number of experts on a low budget; this low budget is important to allow professionals of different countries and situations to attend. At that session, a first edition of the hard copy book will be presented.

3.3: Current activities

3.3.1: Description of current activities

After the closure of the formal contract period (December 15, 2002), the Co-ordinating Centre (UMC Utrecht, the Netherlands) has provided extensive financial and personal resources to enable the completion of the project and ultimate attainment of the goals of the project. Since the dissemination activities are basically provided for, the focus now lays mainly on the completion of the reviews. The following actions have been taking during and after the project to optimise the work in the project:

The two defaulting groups have been redirected. Group 6 have been dissolved and the work has been taken over by the Co-ordinating Centre with the help of a few selected experts. Group 2 has been redirected and supported by active participation by the Co-ordinating Centre. The other three groups have also been redirected by more active leadership from the Co-ordinating Centre with abolishment of the group autonomy that was originally envisaged. These changes, that began in the last half year have had a major impact on group achievement and provide the basis for completion of the project

The editing and completion of the reviews will be dome by the staff at the Co-ordinating Centre.

Reviews will be published on the website with a restricting text as soon as the reviews are ready for publication.

3.3.2: Timetable

The following timetable is in place to achieve the remaining objectives and operational parts:

April 1, 2004: Completion of the reviews
May 1, 2004: Final approval of the reviews by the groups (teleconferencing)
June 1, 2004: Reviews to the printer
August, 2004: Training session and presentation of first hard copy edition

On June 1, 2004 a achievement report will be presented to the Commission and on September 1, 2004 an exit report.

3.4: Dissemination activities

The project leader and the project officer have been invited to a number of activities related to the TEAM-1 project. These are:

1. April 14, 2000: Barrientos ZM. Presentation on the concept and design of the TEAM-approach. Meeting VSOP (patient interest group), den Haag, The Netherlands.
2. December 8, 2000: de Valk HW. Presentation on the TEAM-project, Directorate General Public Health, Luxembourg, Luxembourg.
3. March 26, 2001: de Valk HW. Presentation on the TEAM-study to the International Pharmaceutical L. London, United Kingdom
4. May 9-10, 2001: de Valk HW. Presentation on the TEAM-study in the setting of the Karlskoga meeting on rare diseases, Karlskoga, Sweden
5. May 11, 2001: de Valk HW. Presentation on the TEAM-study to the staff of the Karolinska Institutet, Stockholm, Sweden.
6. November 22, 2001: Barrientos ZM. Presentation on the research in rare diseases in general and alkaptonuria in particular to the Dutch Pharmaceutical Society
7. December 4, 2002 Presentation on rare diseases and the TEAM-approach to the Dept. of Paediatrics of the UMC Utrecht, the Netherlands
8. April 17, 2002 de Valk HW. Presentation on PKU and rare diseases in adult life in the setting of the study Biopharmacy of the University of Leiden, the Netherlands.
9. Octobre 1, 2002: Submission of manuscript on PKU in adult life, related to the TEAM-project for a Dutch book on lifecycle medicine; publication 2003 (or perhaps 2004).
10. Octobre 4, 2002: Dissemination of educational activities in national internist congress, Zeist, the Netherlands
11. November 20-22, 2002 de Valk HW. Presentation at the annual conference on rare diseases in Fulda, Germany, dealing with the results of a Europe-wide query on prevalence of individual diseases and initiatives dealing with the problem
12. November 27, 2002 de Valk HW. Meeting with the Directorate of the ESN (Dutch Society for the Study of Inborn Errors of Metabolism) to start the integration of the educational activities and the TEAM-approach in the education of Dutch internists; this has resulted in a joint educational activity with the Dutch Endocrine Society on November 27, 2003.

13. November 28, 2002 de Valk HW. Presentation to the Societe Francais d'Erreurs Innate Metaboliques. Paris, France.
14. April 22, 2001 Letter announcing upcoming activities in the setting of the TEAM-approach and related educational activities to the Dutch Society for Internal Medicine; positive reply (see also point 9).
15. April 20, 2001 Letter announcing the emergence of educational activities regarding rare diseaes to the SSIEM; no reply. Letter resent lately; no reply yet.

In some of these activities, the focus was solely on the TEAM-effort, in some of them it was part of the presentation or activity, but in all cases with the same aim: presenting TEAM to a wide audience.
The dissemination activities files that have been stored (1,5,7,8,9,10,11,13,14 and 15) and presentations are supplied in an electronic form on the CD-rom.

3.5: Perspective

The current project has outlined that it is possible to organise such a project in Europe, but that specific conditions are required and that such a in-depth project, in contrast to mere description of a disease of logistic information, is a complex phenomenon. On the basis of the experience in the current project, a number of changes has been made to achieve the ultimate objectives and these experiences have been used to adapt the workings of the TEAM-2 project that approaches similar patient groups form a different angle.

4: Conclusions

The TEAM-1 project has a high-profile aim and in the current condition some of the objectives and/or operational parts leading to the ultimate aims have been achieved. The review process and the editing process has been speeded up by more active role of the Co-ordinating Centre at the expense of considerable financial and personal resources by the Co-ordinating Centre. The timetable shows that the training session and the hard copy will be presented in August 2004. These experiences with a Europe-wide initiative using already heavily-loaded experts have led to changes in the conduct of a related EU-funded project (TEAM-2) in order to achieve the goals of that project within the contract period.

4: Participants

Co-ordinating centre

H.W. de Valk	project-leader
Z.M. Barrientos	project-associate
W. Lisman	secretarial assistance

Group 1

H.W. de Valk	Group leader/endocrinologist	UMC Utrecht	Netherlands
Z.M. Barrientos	Researcher	UMC Utrecht	Netherlands
T.J. de Koning	Expert paediatrician	UMC Utrecht	Netherlands
G. Visser	Expert paediatrician	UMC Utrecht	Netherlands

Group 2

A.B. Burlina	Expert paediatrician	Univ Padova	Italy
A.P. Burlina	Expert neurologist	Univ Padova	Italy
Luisa Bonafe, MD	Expert paediatrician	Univ Children's Hospital	Italy
Carlo Dionisi-Vici	Expert paediatrician	Children's Hosp. GESU	Italy

Group 3

J. Leonard	Expert paediatrician	ICH	UK
P. Lee	Expert paediatrician	UCLH	UK
P. Smit	Expert paediatrician	UMCG	Netherlands

Group 4

M. Ugarte	Expert molecular biology	Univ Madrid	Spain
M. Begona	Expert biochemist	Univ Madrid	Spain
Mª José Garcia Muñoz	Expert biochemist	Univ Madrid	Spain
Mª Teresa Garcia-Silva	Expert molecular biology	Univ Madrid	Spain
Mercedes Martínez-Pardo	Expert biochemist	Univ Madrid	Spain
Celia Pérez-Cerdá	Expert molecular biology	Univ Madrid	Spain
A. Ribes	Expert paediatrician	Inst Bioquimica Clinica	Spain

Group 5

Tavares d'Almeida	Expert biochemist	Univ Lisbon	Portugal
R. Parini	Expert paediatrician	Milan	Italy
M Duran	Expert biochemist	UMC Amsterdam	Netherlands
A. Ribes	Expert paediatrician	Inst Bioquimica Clinica	Spain
B-T. Poll-The	Expert neuro-peadiatrician	UMC Amsterdam	Netherlands
F. Ventura	Expert biochemist	Univ Lisbon	Portugal
M. Silva	Expert biochemist	Univ Lisbon	Portugal

Group 6

B-T. Poll-The	Expert neuro-peadiatrician	UMC Amsterdam	Netherlands
B. van Geel	Expert neurologist	Alkmaar Med Centre	Netherlands
D. Chauvau	Expert internist	Hopital Necker Paris	France

5: Activities

In this section, an overview will be given of the sequential activities during the project will be given.

First year of the project
The following activities were done in the first year of the project:

1: Kick-off meeting in Utrecht, the Netherlands involving the group leaders and one deputy
2: Formation of the expert groups
3: Designing the review questions
4: Starting up the review process with selection of papers
5: Progress meeting during the SSIEM-meeting in Prague (Czech Republic) on September 6, 2001 (SSIEM: Society for the Study of Inborn Errors of Metabolism)
6: First design of the educational format
7: First design of the hard copies of the presentation of the quality-assessed expertise
8: Planning meetings in 2002 and further work on review process and training sessions.

These actions will be described in more detail in the next section:

1: The kick-off meeting was held according to plan. The full notes of the kick-off meeting are presented as Appendix B.

2. Formation of the expert groups
Following the kick-off meeting, the experts were instructed to form the expert review groups. Initially, experts could be recruited from the European countries. At a later stage, instigated by discussion during the meeting in Prague, it was decided that it would be better to recruit the final participating members more from one country or from two to three adjoining countries, allowing for one additional meeting of these groups to speed up the progress. The participants in the different expert groups that were formed during the year and the diseases they are to cover are shown in Appendix C from the Prague meeting.

3. Designing the review questions
After the kick-off meeting, the experts should form the expert review groups which would then define the review questions. To speed up the process and to help the individual experts in this process, the co-ordinating centre designed a format into which the questions could be grouped.
This meant that the starting point is the individual disease and that relevant review questions for that specific disease were identified in 5 fields:
1: General questions (prognosis for example)
2: Diagnostic issues
3: Treatment and transition to adult care
4: Complications and monitoring
5: Other issues (pregnancy for example)

The expert review groups received these proposals and were free to change the questions.
The final set of review questions was discussed and agreed upon during the meeting in Utrecht in march 2002, but most work was done during the first year 2001.

4. Starting up the review process with selection of papers
Not all expert review groups proceeded in the same speed. This meant that some groups were already entering the selection phase whereas others were still in the review question design stage. This is no problem, since the deliverables are not expected to come all at once; the individual trainings are given in an extended time frame.
On the basis of broad categories of the review questions, searches into the literature databases were performed and the titles sent to the expert review groups. These did a preliminary selection of the titles.

5. Progress meeting during the SSIEM-meeting in Prague
This meeting was held according to plan; the full notes are given in Appendix C.

6. First design of the educational format
This was discussed during the meetings in the first year and will be decided upon during the second year.

7. First design of the hard copies for the presentation of the quality-assessed expertise
This was discussed during the meetings in the first year and will be decided upon during the second year.

8. Planning meetings in 2002 and further work on review process and training sessions.

Second year of the project
The following activities were done during the second year of the project.

1: Progress meeting in Utrecht, the Netherlands involving the group leaders and one deputy; March 21 to March 23, 2002.
2: Progress meeting during the SSIEM-congress in Dublin (Irish Republic) on September 5, 2002 (SSIEM: Society for the Study of Inborn Errors of Metabolism)
3: Optimising the composition of the expert groups
4: Performing the literature search and provision of materials.
5: Ongoing design of the educational format
6: Preparing the finalising meeting and planning the ongoing and oncoming activities enabling achievement of the deliverables of the project.

These actions will be described in more detail in the next section:

1. Progress meeting in Utrecht, the Netherlands involving the group leaders and one deputy: 21-23 March 2002.
This meeting was held according to plan and the full notes can be found in Appendix D.

2. Progress meeting during the SSIEM-congress in Dublin (Irish Republic) on September 5, 2002 (SSIEM: Society for the Study of Inborn Errors of Metabolism)
This meeting was held according to plan and the full notes can be found in Appendix E.

3. Optimising the composition of the expert groups
Evaluation of the progress of the different groups showed that group 6 (France) was lagging seriously behind and that some readjustment was necessary. In collaboartion with the expert group principal, a new contact person was designated at the composition of the group was changed as well as the content of the group's topics. The new set-up of group 6 is shown in the Appendix E. One (relatively frequent) lysosomal storage disease (m. Fabry) is to be covered by a subgroup of group 6, the more rare lysosomal storage diseases by a subgroup of group 1. The X-linked adrenoleucodystrophy is to be covered by another subgroup of group 6.

4. Performing the literature search and provision of materials.
This has been a continuing process during the year and has been carried out by the Co-ordinating Centre and was concluded before the end of the contract period.

5. Ongoing design of the educational format
This has been done in the second year in preparation for the "Finalising meeting" in February 2003. At that meeting the final decisions were taken and the reader is referred to that section (Chapter 7) for more details.

6. Planning the ongoing and oncoming activities enabling achievement of the deliverables of the project.
This has also been done in the second year in preparation for the "Finalising meeting" in February 2003. This meeting was held at that time (shortly after the end of the formal contract period because it was impoosible to have the participants come together in the months immediately surrounding Christmasand New Year. At that meeting the final decisions were taken and, again, the reader is referred to that section (Chapter 7) for more details. The groups 4 and 5 held separate meetings, detailed in Appendix F and G.

6: Finalising the project

Activities:

The following acticvities were done.

1: Finalising meeting in Utrecht, the Netherlands involving the groups leaders and one deputy, February 6 to Februay 8, 2003.

2: Ongoing and oncoming activities

1. Finalising meeting in Utrecht, the Netherlands involving the groups leaders and one deputy, February 6 to Februay 8, 2003.

The aim of this meeting was to come to the final defition of the end products an deliverables, the final timetable and planning of the activities. A synopsis of the meeting is given here. The full notes can be found in Appendix H.

General remarks

We are working on systemic reviews firstly and not on guidelines.

To involve a larger group of experts in the future developments,: use the Delphi-method of assessments of current opinions with the view of reaching consensus are to be employed *Future meetings (TEAM-2):* to be held form Tuesday night to Thursday afternoon

The topics of the groups were finally designed in this way:

Group 1: Phenylketonuria, alkaptonuria, lysosomal sotrage disorders other than Fabry and Gaucher
Group 2: Homocystinurias, ornithine transaminae C deficiency
Group 3: Glycogen storage diseases I and III, galactosaemia
Group 4: Fatty acid oxidation disorders
Group 5: Organic acidurias
Group 6: X-linked adrenoleucodystrophia, X-linked adrenomyeloneuropathy
Group 7: Lysosomal storage disorders (Fabry, Gaucher)

Report & review

The reviews will be published as a joint effort in a book.

Evidence-based medicine: We are not working on the highest level of evidence-based medicine, but we have worked systematically so we do have to explain which level of evidence this is.

Review of certain area of each disease: can be published separately as a paper, with an acknowledgement of the TEAM project/team; it may not be the exact chapter of the book.

The delivearables:

The form and contant of the hard-copy book are shown in Appendix I.

The form and content of the training sessions are shown in Appendix J.

2: Ongoing and oncoming activities

Since it was shown that the review activities severely lacked behind, a number of measures were taken in the latter part of the year.

- Rearrangement of some of the groups, mainly the abolition of group 6 and choice of new reviewers.
- Introduction of the Co-ordinating Centre as member of each of the working groups

In addition, the website, originally postponed until 2004 in view of the state of affairs, was designed at the end of 2003 with elementary information and linkage to provide some kind of presentation framework.

Contacts with the publisher of the hard copy were strengthened and agreements made for the August 2004 first training session.

7: List of Appendices

A: List of meetings and activities held for the project:
B: Notes of the kick-off meeting February 2001
C: Notes of the meeting Prague, September 2001
D: Notes of the Progress meeting, Utrecht, March 21 to March 23, 2002.
E: Notes of the Progress meeting, Dublin, September 5, 2002.
F: Minutes of the meeting of group 4.
G: Minutes of the meeting of group 5
H: Notes of the "Finalising meeting", February 7 to February 9, 2003, Utrecht.
I: Form and content of the hard-copy book
J: Form and content of the training session
K: Example of review
L: Detailed budget

8: Appendices

A: List of meetings and activities held for the project:

15-2-01 till 18-2-01
Kick-off TEAM meeting in Utrecht present: H.W. de Valk, Z.M. Barrientos, I. Tavarez de Almeida, A.P. Leandro, B. Merinero, A.B. Burlina, J. Leonard.

23-05-01 till 26-05-01
Conference: Prospects in the treatment of rare diseases, Trieste:
H.W. de Valk, Z.M. Barrientos

6-09-01 till 9-09-01
Meeting Prague: Society of the Study for Inborn Errors of Metabolism (SSIEM)
Present: Prof. I. Tavarez de Almeida, Dr. A.B. Burlina, Prof. J-M Saudubray,
Dr. B. Merinero, Dr. Z.M. Barrientos, Dr. H.W. de Valk

9-10-01 till 13-10-01
Conference: IXth international cochrane colloquium, Lyon:
H.W. de Valk, Z.M. Barrientos

6-3-02 till 8-3-02
Conference: Fifth International Symposium on Clinical Advances in Osteoporosis
H.W. de Valk, Z.M. Barrientos

21-3-02 till 23-3-02
In between meeting TEAM in Utrecht: Harold de Valk, Zaira Barrientos, Tom de Koning, Rossella Parini, Isabel Tavares de Almeida, Antonia Ribes, Luisa Bonafe, Carlo Dionisi-Vici, Alberto Burlina,Alessandro Burlina, John Stone, Dorota Johansson

3-9-02 till 8-9-02
Meeting Dublin: Society of the Study for Inborn Errors of Metabolism (SSIEM) TEAM meeting present:Harold de Valk, Zaira Barrientos, Tom de Koning, Rossella Parini, Begonia Merinero, Isabel Tavares de Almeida, Philip Lee, Jean-Marie Saudubray, Antonia Ribes

4-11-02
In between meeting organic aciduria expert group in Madrid: Magdalena Ugarte, Mª José Garcia Muñoz, Mª Teresa Garcia-Silva, Mercedes Martínez-Pardo, Begoña Merinero, Celia Pérez-Cerdá, Antonia Ribes (Barcelona)

17-10 02
In between meeting Portugal: I. Tavares de Almeida (Lisboa, Portugal), M. Duran (Amsterdam, The Netherlands), A. Ribes (Barcelona, Spain), R. Parini (Milan, Italy), F. Ventura (Lisboa, Portugal), M. Silva (Lisboa, Portugal)

7-2-03 till 9-2-03
Evaluation meeting TEAM in Utrecht: Harold de Valk, Zaira Barrientos, Tom de Koning, Philip Lee, Alberto Burlina, Alessandro Burlina, Carlo Dionisi-Vici, Gepke Visser, BeTween Poll The, P. Smit, W. Kleijer.

B: Notes of the kick-off meeting February 2001

List of participants kick-off meeting

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Guests:

Dr. Michael W. Schubert, Engelhorn Foundation For Rare Diseases, 28, Côte dÉich, L-1450 Luxembourg, Tel: +352-2643441, Fax: +352-26434413, E-mail: info@engelhornfoundation.org

Dr. Staffan Stromberg, Swedish Orphan AB, Drottinggatan 98, SE-111 60 Stockholm, Sweden, Tel: +46-8-4028330, Fax: +46-8-4111254, E-mail: staffan.stromberg@swedishorphan.se
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Agenda kick-off meeting

Thursday 15 February till Sunday 18 February

Thursday:		
Morning:	Arrivals and hotel check-ins	
Afternoon:	14:00	-General outline of the meeting: Programme expert groups trainings -Inventarisation of areas of interest and areas of development (area of interest: current care of adults and quality assessment of current expertise)
	15:00	Introduction to methodology of assessment of knowledge
Evening:	Dinner	
Friday:		
Morning:	9:00-12:30	Sessions: methodology, practical examples of quality assessment preliminary outline of expertgroups
Lunch	12:30-13:30	
Afternoon	13:30-15:00	- forming of the groups - discussion
	15:00-18:00	Social programme
Dinner	20:00	
Saturday:		
Morning	Freetime	
Lunch	13:00	
	Session 14:00	-sequence of work -consensus and trainings
	Sessions 15:00	-practicalities, summing up, final conclusions and planning
Dinner		
Sunday:	Departures	

Subjects to be covered by the different expert groups

AMINI ACID I:

Utrecht, The Netherlands:	dr HW de Valk
-Phenylketonuria	dr FJ van Spronsen
-Alkaptonuria	dr ZM Barrientos
-Tyrosinaemia	dr. F.A. Wijburg
	dr. J.B.C. de Klerk

AMINO ACID II:

Padova, Italy:	dr AB Burlina
-Homocystinuria	dr AP Burlina
-Maple syrup disease	dr L Bonafe
-Hyperornithinaemia	dr C Dionisi-Vici

-Urea cycle defects: NAGS, OTC, OTC II, Citrullinaemia, Argininosuccinic aciduria, Argininosuccinate lyase deficiency, Arginase deficiency, CPS

ORGANIC ACIDURIAS:

Madrid, Spain:	prof M Ugarte
-Propionic acidaemia (PA)	dr B Merinero
-Methylmalonic aciduria (MMA)	dr José García Muñoz
-Isovalericaciduria (IVA)	dr. Antonia Ribes
	dr. Celia Pérez-Cerdá

CARBOHYDRATE DISORDERS:

London, United Kingdom:	prof J Leonard
-Galactosaemia	dr P Lee
-Glycogen storage disease	prof Beat Steinmann
-Fructose disorders	dr. S. Schweitzer-Krantz
	dr. GPA. Smit

FATTY ACID DISORDERS:

Lisbon, Portugal:	prof I Tavares de Almeida
-LCHAD	dr A Ribes
-MCAD, LCAD, SCAD, vLCAD	dr R Parini
-MTP	dr M Duran
-MADD	dr U Caruso
-CPT	
-vLCAD	

-Carnitine acylcarnitine translocase deficiency

OTHER DISORDERS:

Paris, France	prof. J.M. Saudubray
-ALD	dr. D Chauveau
-Lysosomal disorders	dr T Billette de Villemeur
-Peroxisomal disorders	prof P Aubourg
	prof BT Poll-The
	dr N Belmatoug

Notes: kick-off meeting, February 15-18, 2001

Introduction:
During this meeting, all experts from the six groups and one deputy were invited to the meeting. The actual participants to this meeting are listed in Appendix A.
The aim of the meeting was to establish the mutual relations and describe the situation in each centre, to define the elementary objectives and deliverables of the project, to discuss the essential features of the review process and the content and form of the training sessions.
The agenda of the three-day meeting is shown in Appendix B.
Summarising the main outcomes of the meeting:
-the subjects of each review group were divided amongst the participants. The final subjects for each group are shown in Appendix C.
-the methods for literature review of the Cochrane method were adopted as leading principles and applied when possible
-original research papers and case-reports will be studied primarily together with reviews, the latter mainly for identification of references
-abstracts will not be included
-the main European languages in the EU will be considered; papers in other languages will be evaluated when an English abstracts is available; if the paper is deemed worthwhile, the paper will be translated
-review questions will be orientated to clinical problems and dilemmas
-literature search will not extend to before the year 1966
-review groups will be formed according to the wishes of the experts; formal invitations by the co-ordinating centre
-the forms used for selection and appraisal of the papers were discussed already
-all selected papers will be registered in a Reference manager database in the Co-ordinating Centre to allow accountability and to have permanent identification of selected and rejected papers.
-initiatives were discussed to organise the trainings and to extent the generated knowledge into a more long lasting system of Europe-wide education on rare metabolic diseases in adulthood; contact with professionals societies including the Society for the Study of Inborn Errors of Metabolism will be sought.

Notes:
Dr de Valk welcomes everybody and explains the aim of this meeting.

This is followed by a short description by each centre of problems encountered when dealing with the specific patient group. The diagrams of Prof. Leonard (London) and Dr Burkina (Padua) are included in the slide handout of the meeting.

Some problems are common to all centres:
to whom do you send the patients when they become adults
how to transfer the patients from one department to the other
diets are very difficult to explain to patients and are difficult to integrate in normal daily life
how to communicate with the severe retarded patients

After a short break, the following session was dedicated to “Introduction to methodology”
The diagram series prepared by the co-ordinating centre (UMCU) served as guide and are included in the slides handout of the meeting.
The following items were discussed:

The aim of the project is to create a database of information on diagnosis, treatment, complications and prognosis in adult patients with rare metabolic diseases. The core of the project is quality assessment of current expertise and the subsequent design of specific training’s of which a first try-out will be performed in this project.

An important item of the quality assessment is the implementation of the systematic review
This means:
Systematic review of current expertise: systematic review of publications
Systematic means:
-adequate and comprehensive search strategy
-accountability of inclusion or exclusion
-reproducibility of inclusion or exclusion
Applies to all types of studies

Systematic reviews
1: Unit of research: publication
2: Definition of a research question
3: Definition of the search strategy
4: Accountability of inclusion non-inclusion: *selection*
5: Judgement on the merits of publications: *appraisal*
6: Transparent presentation of the results: review

The central item of a systematic review is the prevention of bias as much as possible

1: Publications to be used
Randomised controlled clinical trials
Non-randomised clinical trials
Observational studies
Case-reports
"Expert opinion"

Results of discussion
→ Abstracts will not be used
→ All modern languages will be included (English, German, French, Spanish, Italian, Portuguese, Dutch); Japanese after reading of the english abstract
→ All kinds of studies may be included, but case-reports will mainly be used as source for review questions and source for references (hand-picking)

2: Definition of the review question

The specific review question determines search strategy
The better specified the question, the more tailored the search strategy
More than one question on a specific item is possible
Examples of items on which reviews questions can be based:
-Epidemiology of the disease (prevalence)
-Causes and genetics
-Clinical presentation
-Diagnostic procedures
-Therapeutic interventions and strategies
-Prognosis

Review questions determines also the most appropriate type of study for that item
-randomised clinical trial
-non-randomised clinical trial
-observational study
-case-report
Review question is the starting point (expert group); to be filled in on a special sheet.

3: Search strategy

Based on the specific review question
Different items:
-indication for a therapy
-intervention
-type of publication
-combination of the above

Sources of literature
Electronic database -Medline
-Embase
-others

Screening of references (hand-picking)
Specific databases
Other strategies secondary search strategy (other items)

Results form discussion
→ keywords as complete as possible
→ the co-ordinators decide on the search strategy to ensure uniformity
→ period 1966 till now; older important ones can be found through the references in the publications

4: Selection of publications

Selection of publications:
In/exclusion criteria for instance: -age
-sex
-intervention
-follow-up duration

Transparent selection on predesigned form
Entry of all publications in *Reference manager* by co-ordinating centre; this includes also publications you do not select: no double work later and accountability of the process.
Minimally two reviewers for any publication.

5: Judgement of the publication (appraisal)

Internal validity (quality of the publication)
External validity (extrapolation to other subjects with this disease)
Quantitative aspects (data presentation)
Other relevant items encountered
Major items in the appraisal of the publications:
-Description of the studied population
-Diagnostic procedures
-Randomisation
-Study intervention
-Assessment
-Follow-up
-Side-effects

6: Transparent presentation of the results
Review: -qualitative data
-quantitative data: meta-analysis

Types of study:
Controlled clinical trial
Rationale
⇒ -assessing the effects of an intervention against no intervention or another intervention while controlling for possibly interfering (confounding) factors: **randomisation**
-controlling only for known (and implicitly unknown) confounding factors by randomisation
-controlling for choice of intervention by physician and/or patient
-not only in curative, but also in preventive medical setting
Items to be considered:
Patient population studied (inclusion/exclusion); extrapolation of the results
Intervention A
Intervention B
Effect parameter(s)

Selection form
Appraisal form
-Non-randomised clinical trial

⇒ -when the natural history is known (historic controls) and is associated with severe morbidity or early death
⇒ -when there is evidence of a beneficial effect: pregnancy
⇒ -toxicity and side effects of the drug are known and acceptable
⇒ -when there are easily and reliably assessable end points
⇒ -when toxicity and side effects are easily and reliably assessable

But

⇒ -the natural history may be highly variable
⇒ -confounders are not accounted for (known/unknown factors)
⇒ -laboratory success or success in soft/biochemical end points may not be translated into success on hard clinical end points

Observational study
-cross-sectional
-prospective
-retrospective
-case-control
-cohort/follow-up

Observed associations
-outcomes (end points) over time
-determinants of outcomes
-factors influencing outcomes

Problems with longitudinal observations
-selective inclusion: silent disease, late onset, incorrect diagnosis); incomplete ascertainment:
→**underestimation**
-frequency genotype >> Frequency phenotype
-selective drop-out
Danger ≡ exaggerated positive/negative outcome/correlation
≡ diminished positive/negative outcome/correlation
Solution ≡ comparing baseline data from those remaining in study with those dropping out of the study
-cohort effect (coronary heart disease 1960 ≠ 2001)

Observed associations
-causal relation?
-chance association?
-both related to a common "cause"?
Associations between parameters in a cross-sectional study are not necessarily causally related
Interpretation also depends on inclusion characteristics.

-Case-reports
Problems with case-reports
-New disease?
-Collection of exceptional patients?
-Publication of a patient with a very rare disease?
-Quality and completeness of the data?
-Corroboration of the new finding in other patients?
-Data from "old" literature?
-Coincidence?

Results of the discussion:

→ The most review questions will be about treatment and prognosis; for these reviews we can let out the case-reports; inclusion for references only

→ If the expert group decide to use case reports, that has to be written beforehand in the protocol

→ Consensus: use case-report for biochemical diagnosis; for clinical, therapeutic and prognosis leave them out; if you use them you will have to come up with arguments

→ Review papers: Inclusion for references only

In summary:
-Definition of the review question, leading to writing of the review protocol, including type of trial, key words, sources, selection criteria, appraisal criteria and outcome; these data will be pooled and presented. The co-ordinating centre will take care of a uniform review protocol, search strategy, refining (if necessary) of the review question and providing of literature; later pooling of data and presentation.

Important is the formation of the expert groups:
-Each expert handles one group (see list)
-Each group consists of subgroups according to disease, headed by a subgroup-head
-Experts may join other subgroups as subgroup-head or as member
-Other members by invitation
-Other members by publication, inviting subjects to apply for membership. Participation of a specific individual will be decided upon by the expert group head
-Multilingual composition

The trainings themselves:
Discussion centred on whom to target, how to advertise, accreditation.

Saturday February 17, 2001
Examples review questions and problems encountered

LONDON

Galactosaemia:

- complications:	is there evidence of loss of cognitive skills in adults
	what is the prevalence of ovarian failure
	what is the prevalence of osteoporosis
- treatment:	how strict should the diet be
	evidence for the use of RBC-Gal-1-p

Question: should we exclude alfa-galactosides

Hereditary fructose intolerance:

- diagnosis:	is molecular diagnosis reliable for fructose intolerance
- treatment:	how strict should the diet be

Fructose-1-6-diphosfonase deficiency:

- treatment:	is a fructose-free diet really necessary

Glycogen storage disease:
Type I:

- complications:	what is the prevalence of chronic renal failure
	what is the prevalence of osteoporosis and its complications
- treatment:	what is the optimal treatment in adults

Type IB:

- complications:	what is the prevalence of inflammatory bowel disease
	what is the prevalence of infections
- treatment:	what are the complications of GCSF
	is there a treatment/therapy for IBD

Type III:

- complications:	what is the prevalence of disabling myopathy
	what is the prevalence of symptomatic myopathy
- treatment:	what is the optimal treatment: HCGH protein diet or others

PORTUGAL

FFA oxidation disorders:
the reliability of metabolic profiles in diagnosis of FFA oxidation disorders
to assess fatty liver disease in pregnancy
the prevalence of FFA oxidation disorder in fatty liver and pregnancy
treatment: carnitine??; biochemical?? ; follow-up

Fatty acids:
-later onset defects to diagnosed this
-fatty liver in pregnancy
-risk of complications in pregnancy, screening in HELLP syndrome??
-carnithine therapy controversy, biochemical follow-up
-adult patients developing steathosis???? Proper investigation

ITALY

Homocystinuria:
-to define the safety value of total plasma homocysteine in treated patients
-to investigate the long-term complications (like osteoporosis and neurological complications) in treated patients
-to investigate the efficacy of betaine treatment
Urea cycle defects:
-to investigate the diagnostic value of allopurinol test in female OTC deficiency
-to investigate the efficacy of phenylbutyrate treatment in patients with UCD
-to investigate efficacy of liver and hepatocyte transplantation therapy
Hyperornithinaemia:
-to evaluate the frequency of spastic paraplegia in HHH syndrome
-to investigate the efficacy of lysine / creatine therapy in gyrate atrophy
Maple syrup disease:
-to investigate the long-term complications in early treated MSUD patients
-to investigate the efficacy of valine/isoleucine supplement in the diet
problems: same patients with different treatment, too many variables.
-find crude data for better analysis

SPAIN

MMA:
-in non-responsive patients: to investigate if transplantation of either kidney or liver or both simultaneously is the final solution for survival
-to evaluate the natural history of renal disease in MMA
-to find out the best clinical and biochemical data for follow-up
in MMA and homocystinuria: to evaluate the clinical complications
AP and IVA:
-to evaluate if early diagnosis may result in a different outcome concerning neurogical problems and quality of life
-to evaluate if early treatment may result in a different outcome concerning neurogical problems and quality of life

Other BCDA:
-to evaluate the clinical complications in ß-ketothiolase deficiency
-to evaluate correct diagnosis by performing metabolites studies in these other diseases
-treatment: to evaluate the protein amount
to evaluate the safety of amino acid mixtures
to evaluate the different doses of treatment

C: Notes of the meeting Prague, September 2001

Attending:
Prof. I. Tavarez de Almeida
Dr. A.B. Burlina
Prof. J-M Saudubray
Dr. B. Merinero
Dr. Z.M. Barrientos
Dr. H.W. de Valk

Absence with notification:
Dr. P. Lee
Prof. Leonard
Prof. M. Ugarte
Dr. A.P. Burlina

Introduction:
This meeting was meant to monitor the progress of the project and only the experts and the co-ordinating centre were invited to participate. The actual list of participants is given in Appendix E. It was decided that:
-the then present review questions –prepared by the Co-ordinating Centre- were too broad and should be narrowed done. This was to be done by the experts and the expert review groups themselves.
-it would be better to construct an expert review group with members form the same and adjoining countries, to allow one extra group meeting to discuss the literature and come to a consensus. This consensus would then be discussed in the large plenary meeting at the end of 2002. At that meeting, the final scientific content of the project and the trainings will be determined and constructed. This consensus then is the basis of the trainings.
-to have three training sessions, each dealing with two of the six item groups. The form of the training will be discussed with the relevant educational professionals and authorities
-the deliverables are essentially the set of trainings and the hard and electronic copies of text of the quality-assessed literature. The aim is to discuss publication as hard copy with journals and/or publishing houses.
-in view of the desire to strengthen the long-term European training perspective, each expert should provide the Co-ordinating Centre with the addresses of the relevant authorities in each country.

Notes:
De Valk opens the meeting at 1.00 pm and welcomes the participants to this meeting. The following items were discussed.

Current situation of the TEAM-1-project
Review questions
Every group has received the preliminary example questions from the Co-ordinating Centre. Burlina remarks that the questions are rather broad and need to be narrowed down in order to prevent undue amounts of publications to be dealt with. This view is endorsed and it is agreed to have a more narrowed down list of review questions by the end of the month September prepared by the expert-heads and send to the Co-ordinating Centre.

Members of the groups
The list of participants in the expert groups is then discussed. Tavarez de Almeida remarks that face to face meetings would be necessary to have a good and fast discussion, discussing through email would take up much more time and slow the process down. This point is discussed and accepted. The actual proposal is to form expert groups with members from a certain geographical area to allow an in-between meeting. This would mean that the members from a certain group live within a reasonable distance (not necessarily the same country) as the expert head. Group size ideally would not exceed five members. Far-off members are allowed but not too many. Already invited members stand. It is decided that there will be a complete group meeting in February 2002 to evaluate the progress. Important to note is that all the groups have one possibility to organise a meeting with their members to speed up the process, either before or after the February 2002 meeting.

Time table
The following time table is agreed upon:
October 1, 2001: return focussed review questions to Co-ordinating Centre
January 1, 2002: receipt of the literature abstracts from the Co-ordinating Centre
21th-24th February 2002: proposed date meeting in Utrecht
October 2002: consensus meeting:

Training sessions
Discussion on this subject is ongoing. The idea is to deal with a number of groups in a separate training (for example group 1-3 in one training and 4-6 in a separate second one). Ideas about the actual training methodology (lecture, working groups, hands-on training, case-reports etc) are welcome.

End products
The Co-ordinating Centre will investigate the possibilities of publishing the results of TEAM through various means:
-separate appendix to a journal
-separate book
-others

European training
This point is shortly touched upon. All the participants are asked to supply information and addresses of governmental and non-governmental institutions who could be involved in setting up an European training programme.

TEAM-2
An preliminary text has been written for an extension of TEAM, called TEAM-2. This version will deal with topics of a general nature (transcending the boundaries of individual diseases). The following 6 items are tentatively selected:
-Pregnancy and childbirth
-Bone disease
-Visual problems
-Neurologic manifestations
-New and emerging therapies (cost-effectiveness!)
-Implications of extended neonatal screening

Contrary to earlier information, the deadline is October 30, 2001! You will hear more in the near future.
The meeting is closed at 2.30 pm.

DON'T FORGET
-to send back the focussed review questions in the coming weeks
-select the members of your group and send the names to the Co-ordinating Centre so we can invite them formally
-supply information and addresses of governmental and non-governmental institutions who could be involved in European training programmes
-suggest publishing possibilities
-check your agendas for the meeting in February

If you would like to consider a small meeting with your review-group please let us know, with an estimation of the costs.

D: Notes of the Progress meeting, Utrecht, March 21 to March 23, 2002.

Programme of the Progress meeting, Utrecht, March 21 to March 23, 2002

TEAM-MEETING: TRANSFER OF EXPERTISE ON RARE METABOLIC DISEASES IN ADULTS

Thursday 21th of March till Sunday 24th of March 2002

Programme

Thursday:		
Morning:		Arrivals
Afternoon:	13:00	Lunch "Room KE04 128.0"
	14:00	Introduction to the TEAM-study and general outline of the meeting, dr H.W. de Valk
	14 :30	Review process
	15:00	Coffee
	15:30	Discussion
Evening:	20:00	Dinner "Anak Depok"
Friday:		
Morning:	9:00	The review process: a practical example
	10:30	Coffee
	11:00	Feedback and plenary discussion
	12:00	Lunch Restaurant WKZ
Afternoon	13:00	Workshop in separate groups
Evening:	18:00	Social Programme + Dinner
Saturday:		
Morning	10:00	Feedback and plenary discussion
	12:30	Lunch Restaurant WKZ
Afternoon	13:30	Integrated summing-up
	15:00	Free shopping time
Evening	18:00	Dinner "Ouzeri Eleni"
Sunday:	Departures	

Workshop venue:

University Medical Center Utrecht
Location WKZ
Room KE04 128.0
Lundlaan 6
3508 AB Utrecht
The Netherlands

Hotel:

Hotel de Biltsche hoek
De Holle Bilt 1
3732 HM De Bilt
The Netherlands
Phone: +31-30-2205811

Organizers:

Zaira M. Barrientos
Mobile-phone: 06-22446910

Harold W. de Valk
Mobile-phone: 06-29093307

Notes of the Progress meeting, Utrecht, March 21 to March 23, 2002.

Participants: Harold de Valk, Zaira Barrientos, Tom de Koning, Rossella Parini, Isabel Tavares de Almeida, Antonia Ribes, Luisa Bonafe, Carlo Dionisi-Vici, Alberto Burlina,Alessandro Burlina, John Stone, Dorota Johansson

Introduction:
During this meeting, all experts from the six groups and one deputy were invited to the meeting. The aim of the meeting was to review the progress in the six expert groups formed during the first year of the project, to see if adjustments were necessary to improve the project and to plan the upcoming activities.
A number of comments were made and a number of changes were proposed and discussed:

A: It proved logistically difficult to be working in an expert group including persons spread widely in Europe: communication by e-mail is possible but there is an essential element of face-to-face discussion. The participants felt more at ease with a more regional construction of an expert group with the possibility of assessment of the final products of an expert group by a wider circle of experts. This change was accepted and the group composition adjusted.

B: The importance was stressed to all participants that review questions and the review answers were meant to be clinically-orientated, aimed at helping the medical professionals with commonly encountered problems in the diagnosis and treatment of adults with rare metabolic diseases.

C: A number of operational decisions were made:

Search

Interval of literature: 1977-february 2002: there will be an update in the future before the start of the training (deliverable) so as to exclude the possibility of having missed the latest information.

Key words are broadly defined (disease and another item): diseases will be entered as individuals diseases and using the different synonyms and name of enzymes. Lists of titles will be provided by review question and on demand as all available literature.

Selection

Impact factor should not influence selection decision

Inclusion by majority voting (≥50% of positive votes in the group)

For reviews: only the reference list will be provided

Guidelines will be used to create tables of frequencies, target values etc.

Comments and round table discussions are excluded

Individual groups can request to select on full text instead of on the basis of abstracts: they should score whether they would have included or excluded on the basis of the abstract only as internal control system.

Report & review

The trainings (the products of TEAM) will be published as a joint effort in a book and/or set of reviews and/or the Internet. All reviews will have roughly the same structure and are preceded by an introductory lecture. The format will be made by the co-ordinating centre.

This is a non-commercial project: industry may be guests at the utmost.

All products of meetings and trainings are the joint property, both intellectually and financially, of the TEAM-participants. If joint trials with industry will follow TEAM, this will be discussed at the appropriate time with the group(s).

Initial steps for accreditation of the trainings will be set.

Search in every country for relevant funding agencies in the future for the trainings. The European situation regarding the care for patients with rare inborn errors of metabolism will be assessed by questionnaire in the setting of an unrelated annual scientific meeting in Fulda (Germany) in November 2003.

Notes:
De Valk opens the meeting at 1.00 pm and welcomes the participants to this meeting. The following items were discussed.

General remarks
Review process and creation of the training must be aimed at transfer and discussion of clinically-relevant issues for medical professionals.
Groups are now composed of regional experts; this allows groups to organize one discussion meeting in their own region. Every member of a group deals with all subjects and literature of that group.

Search
Interval of literature: 1977-february 2002; there will be an update in the future before the start of the training so as to exclude the possibility of having missed the latest information.
Key words are broadly defined (disease and another item); diseases will be entered as individuals diseases and using the different synonyms and name of enzymes.
Lists of titles will be provided by review question and on demand as all available literature.

Selection
Impact factor should not influence selection decision
Inclusion by majority voting (50% of positive votes in the group)
For reviews: only the reference list will be provided
Guidelines will be used to create tables of frequencies, target values etc.
Comments and round table discussions are excluded
Individual groups can request to select on full text instead of on the basis of abstracts; they should score whether they would have included or excluded on the basis of the abstract only as internal control system.

Appraisal
After the meeting, we composed a scoring system (points) for the relative value of different papers and study designs. Please may we have your comments!
Quality score for different studies:

	RCT	*Non-RCT*	*Observational*
Randomisation	*0-2*	*----*	*----*
Blinding	*0-2*	*----*	*----*
Accountab inclusion	*0-1*	*0-1*	*0-1*
Outcome	*0-2*	*0-2*	*0-2*
(0=inapp, 1=bioch, 2=clin)			
Adeq. controls	*----*	*0-1*	*0-1*
Follow-up > 1 year	*----*	*----*	*0-1*

Report & review
The trainings (the products of TEAM) will be published as a joint effort in a book and/or set of reviews and/or the Internet. All reviews will have roughly the same structure and are preceded by an introductory lecture. The format will be made by the co-ordinating centre.
This is a non-commercial project; industry may be guests at the utmost.
All products of meetings and trainings are the joint property, both intellectually and financially, of the TEAM-participants. If joint trials with industry will follow TEAM, this will be discussed at the appropriate time with the group(s).
Initial steps for accreditation of the trainings will be set.
Search in every country for relevant funding agencies in the future for the trainings.
The European situation regarding the care for patients with rare inborn errors of metabolism will be assessed by questionnaire in the setting of the SHS-meeting in Fulda this November.

Timetable & deadlines
May 1: Final date to return selection of papers on the basis of the abstracts
June 1: Final date for the co-ordinating centre to send the papers to the expert groups
June-October: Period for the expert groups to appraise the papers, have a separate meeting and begin writing the concept text
November 1: Final date to send concept text to co-ordinating centre
Nov 27-Dec 1 Proposed date for evaluation meeting (please check your agenda and let us know by not later than May 1 if the date is suitable)
Dec 1- 02 to
Feb 1-03: Preparation of the final training text by the co-ordinating centre.
March 1: Final date to send comments to co-ordinating centre.
April 1: Launch of the final TEAM-results
April 1-Dec Trainings

At the moment we are awaiting the final selection results of the groups on the basis of the titles of the papers; we then send the appropriate papers as soon as possible.
We hope to see you in Dublin and later at the next TEAM-meeting.

E: Notes of the Progress meeting, Dublin, September 5, 2002.

Present: Harold de Valk, Zaira Barrientos, Tom de Koning, Rossella Parini, Begonia Merinero, Isabel Tavares de Almeida, Philip Lee, Jean-Marie Saudubray, Antonia Ribes

Introduction:
This was a meeting in during the SSIEM-congress. The aim of the meeting was to monitor the progress of the various groups, identify problem areas as well as specific wishes of the participants, and to plan the future activities in more detail. Important aspects of the proceedings are detailed here.

End objectives of the TEAM-1 project
There was an extensive discussion on the end objectives of the project and the best ways to achieve these objectives and how to optimally reach the intended beneficiaries of the project. The end objectives were adjusted and defined more sharply and in more detail: *T*
he primary end objective of TEAM-1 is a hard copy of the reviews, published as a book. This book is the basis for the training sessions but allows professionals, who are not able yet to attend the training sessions, access to information. Using a book obviates the need for professionals to have modern information technology equipment.
The secondary objective is a set of training sessions based on the quality-assessed literature. The number of specific sessions will be determined by a logical theoretical design of the content of the training session.
The third objective is the electronic dissemination of the knowledge (reviews and training sessions) through the Internet. Current thinking is to first establish one webpage with essential information on content and addresses. This webpage (which can possibly provide on the UMC U-site) is named the "TEAM-page" and linked to webpage/internet-sites of all the major participants of the TEAM-project. The possibility of a link with SSIEM will be explored.
General remarks
Every group can organise an in-between meeting to make the review before the "Finalising meeting" in February. Each group can decide the number of specific diseases they want to cover.
Report and review
The reviews will be published as a joint effort in a book. We have approached a publisher for this: Lemma.
All reviews will have roughly the same structure and are preceded by an introductory section. The format of the reviews will be made by the co-ordinating centre.
Training sessions

Maximum of 25 participants
*Aiming a*t two different sessions
Mechanism of education and teaching: problem oriented, short introductions, case-presentations presentations, involvement of real patients?
Don't forget the unique feature: quality-assessed literature as basis of the training; let's not duplicate existing courses.

Notes:
General remarks
Every group can organise an in-between meeting to make the review before the evaluation meeting in February (see "Report & review).
Each group can decide the number of specific diseases they want to cover. For example, Italy will especially on homocystinuria whereas Portugal will do all the suggested diseases (fatty acid oxidation disorders).

Report & review
The reviews will be published as a joint effort in a book. We have approached a publisher for this: Lemma. See point 1 of the "End Objectives".
All reviews will have roughly the same structure and are preceded by an introductory section . The format of the reviews will be made by the co-ordinating centre.
Expert groups can organise one separate meeting in the coming months, but before February 2003!

The first draft of the review must be made at the separate meeting of the expert group. An example of a format will be send soon!

Training sessions
A number of remarks has been made:
Maximum of 25 participants
We aim at two different sessions
Who will be the audience? Learned Professionals? Starters? Students?
Don't forget the unique feature: quality-assessed literature as basis of the training.
Mechanism of education and teaching: problem oriented, short introductions, case presentations, maybe involvement of real patients
Let's not duplicate existing courses

End Objectives
The primary end objective of TEAM-1 is a hard copy of the reviews, published as a book. This book is the basis for the training sessions but allows professionals, who are not able yet to attend the training sessions, access to information. Using a book obviates the need for professionals to have modern information technology equipment.
The secondary objective is a set of training sessions based on the quality-assessed literature. The number of specific sessions will be determined by a logical theoretical design of the content of the training session.
The third objective is the electronic dissemination of the knowledge (reviews and training sessions) through the Internet. This has run in some financial difficulties since the co-sponsor The Engelhorn Foundation has liquidated itself. Current thinking is to first establish one webpage with essential information on content and addresses. This webpage (which can possibly provide on the UMC U-site) is named the "TEAM-page" and linked to webpage/internet-sites of all the major participants of the TEAM-project. The possibility of a link with SSIEM will be explored.

Action list
Exploration website possibilities (UMC U)
Exploration SSIEM-link (UMC U in conjuntion with the group heads).
Inventory of current courses (UMC U)
We need a cost estimate from every group for the separate meeting and the date it will be held.

Timetable & deadlines
Meeting February 2003: 7-9 February 2003
First training session: june 2003: 5-8 june or 12-15 june
Second training session: octobre 2003

ALL REMARKS AND SUGGESTIONS ARE WELCOME!

New composition of group 6.

OTHER DISORDERS:

X-ALD :

B-T. Poll-The	Expert neuro-peadiatrician	UMC Amsterdam	Netherlands
B. van Geel	Expert neurologist	Alkmaar Med Centre	Netherlands
D. Chauvau	Expert internist	Hopital Necker Paris	France

GSD:

T.J. de Koning	Expert paediatrician	UMC Utrecht	Netherlands
G. Visser	Expert paediatrician	UMC Utrecht	Netherlands

Invitation lectures for:
Lysosomal disorders
Peroxisomal disorders

F: Minutes of the meeting of group 4.

TEAM project

Organic Acidurias

Meeting in Madrid 4th November 2002

Group Members:

Magdalena Ugarte (Madrid, Spain)
Mª José Garcia Muñoz (Madrid, Spain)
Mª Teresa Garcia-Silva (Madrid, Spain)
Mercedes Martínez-Pardo (Madrid, Spain)
Begoña Merinero (Madrid, Spain)
Celia Pérez-Cerdá (Madrid, Spain)
Antonia Ribes (Barcelona, Spain)

Summary of the Meeting
A draft of a review paper, focusing on adult presentation and adult complications of the most frequent organic acidemias (isovaleric acidemia, propionic acidemia, methylmalonic acidemia ± homocystinuria) was made. Glutaric aciduria type I was not included. All the group members will be co-authors.

The scheme of the review is as follows:

Biochemistry of branched-chain amino acids metabolism and of the lysine catabolism (C. Pérez-Cerdá, B. Merinero)
Clinical presentation of each disease (M.T. Garcia-Silva, M. Martínez-Pardo)
Diagnostic strategies for each disease (marker metabolites, enzyme determinations, genetic studies)
IVA: M.J. Garcia Muñoz
PA: C. Pérez-Cerdá
MMA: B. Merinero
Therapy (diets, drugs, tissue transplantation,…). Which parameters are useful for metabolic control? (M.T. Garcia-Silva, M. Martínez-Pardo)
Prognosis + adult presentation + adult complications for each disease:
IVA: M.J. Garcia Muñoz
PA: C. Pérez-Cerdá
MMA: B. Merinero
Pregnancy (each disease)

We hope to be able to produce a manuscript before February 2003.
This review could be later used for the Training Sessions.

G: Minutes of the meeting of group 5

TEAM STUDY PROJECT

Fatty Acids Tranport and Mitochondrial Oxidation Disorders
Sub-Group Meeting
Lisboa, 17 – 18 October 2002

Group Members:
I. Tavares de Almeida (Lisboa, Portugal)
M. Duran (Amsterdam, The Netherlands)
A. Ribes (Barcelona, Spain)
R. Parini (Milan, Italy)
B. Poll-The (Amsterdam, The Netherlands)
C. Vianey-Saban (Lyon, France)
U. Caruso (Genova, Italy)
F. Ventura (Lisboa, Portugal)
M. Silva (Lisboa, Portugal)

Apologies for absence:
B. Poll-The (Amsterdam, The Netherlands)
C. Vianey-Saban (Lyon, France)
U. Caruso (Genova, Italy)

Summary of the Meeting
According to the minutes of the Dublin meeting (attached file) a draft of a review paper, focusing on adult presentation and adult complications of FATMO, was made.

A provisional title was made: ' Fatty acid oxidation defects are growing up: implications for adult age'. All the group members will be co-authors.

The outline of the review is as follows:
Introduction + Biochemistry + Physiology (M. Duran)
General symptomatology, based on tissue-oriented data (liver, muscle, heart, etc.) (R. Parini)
Description of the general aspects of the various known defects, grouped in such a way that common denominators become clear.
Carnitine uptake defect (I. Tavares + F. Ventura)
CPT I deficiency (B. Poll-The)
CACT, CPT II, VLACD, MTP (R. Parini)
MCAD, MAD; HMG-COA synthase + lyase (I. Tavares + F. Ventura)
SCAD-deficiency (C. Vianey-Saban)
SCHAD (M. Silva)

Diagnostic strategies, including all laboratories approaches + *in vivo* testing (A. Ribes + I. Tavares)
Treatment + related aspects (B. Poll-The); drugs interfering with the beta-oxidation (M. Silva)
Prognosis + adult presentation + adult complications. All defects are treated in detail. This will in particular be based on the available literature. We have the feeling that some essentials are still missing. The following arrrangements have been proposed:

CUD (F. Ventura)	CPT I (B. Poll-The)
CACT (R. Parini)	CPT II (U. Caruso)
VLCAD (A. Ribes)	MTP (M. Duran)
MCAD (F. Ventura)	SCAD (C. Vianey-Saban)
SCHAD (M. silva)	HMG-CoA Synthase (F. Ventura)
HMG-CoA Ligase (F. Ventura)	MAD (F. Ventura)

We hope to be able to produce a manuscript by early February, so as to present it at the next TEAM-meeting.

H: Notes of the "Finalising meeting", February 7 to February 9, 2003, Utrecht.

Programme of the "Finalising meeting", February 7 to February 9, 2003, Utrecht.

TEAM-MEETING: TRANSFER OF EXPERTISE ON RARE METABOLIC DISEASES IN ADULTS

Friday 7th of February till Sunday 9th of February 2003

Programme

Friday:		
Morning:		Arrivals
Afternoon:	12:000	Lunch "Room KE04 128.0"
	13:00	Introduction and general outline dr H.W. de Valk
	13 :30	Individual Brainstorming session
	14:00	Design hard copy /book in detail (topics and paragraphs)
	16:00	Discussion design hard copy /book (if not finished we continue in the morning)
Evening:	20:00	Dinner "Ostrich Cafe"
Saturday:		
Morning:	9:00-10:30	Detailed design of training session
	10:30-11:00	Coffee
	11:00-12:00	Detailed design of training session
	12:00-13:00	Lunch Restaurant WKZ
Afternoon	13:00-16:30	Shape and content of personal contribution Assignment of duties Publication policy PR Future plans for an education facility Feedback and discussion
Evening:	18:00-23:00	Dinner (individually)
Sunday:	Departures	

Workshop venue:

University Medical Center Utrecht
Location WKZ
Room KE04 128.0
Lundlaan 6
3508 AB Utrecht
The Netherlands

Hotel:

Hotel de Biltsche hoek
De Holle Bilt 1
3732 HM De Bilt
The Netherlands
Phone: +31-30-2205811

Organizers:

Zaira M. Barrientos
Mobile-phone: 06-22446910

Harold W. de Valk
Mobile-phone: 06-29093307

Present: Harold de Valk, Zaira Barrientos, Tom de Koning, Philip Lee, Alberto Burlina, Alessandro Burlina, Carlo Dionisi-Vici, Gepke Visser, BeTween Poll The, P. Smit.

Notes TEAM-meeting, Utrecht, 7-8 Fberuary 2003

General remarks
To set a clear endpoint during this meeting.
Are we working on systematic reviews or guidelines?
Do we nee a scoring system or is the delphy approach enough
All meetings in the future from Tuesday night till Thursday afternoon
The groups:
Group 1: PKU, AKU
Group 2: Homocystinurias, OTC
Group 3: GSD I and III, galactosaemia
Group 4: FAO
Group 5: Organic acidurias
Group 6: X-ALD/AMN
Group 7: Fabry, Gaucher, MPS

Report & review
The reviews will be published as a joint effort in a book.
We are not working on the highest level of EBM, but we have worked systematically so we do have to explain which level of evidence this is.
A review of certain area of each disease (not the chapter of the book) can be publishes separately as a paper, with an acknowledgement of the TEAM project/team

Hard copy: book
First define who will buy the book:
Think about a title
Example of the size of book= Clark
Foreword of James Leonard en Jean-Marie Saudoubray
Color of the book? Depends on the publisher, otherwise white.

General Format of book:

BIOCHEMICAL PATHWAY TABLE

1. Introduction	disease pathophysiology clinical presentation essential diagnostics: 2 or 3 sentences
2. Therapy	diet or pharmacology or other targets and monitoring
3. Complications	frequently or rarely seen (table or text) treatment and monitoring of complications
4. Fertility issues	fertility, contraception and pregnancy (and outcome)
5. Psychosocial issues	quality of life, profession and so one
6. Summary	key messages, possible future developments, controvercial issues, *justification of sources*
7. References	for introduction use 1 or 2 review or books(fernandes, scriver) a list of the main papers (format reference manager)

Training sessions
A number of remarks has been made:
Maximum of 25 participants
We still aim at two different sessions
Training about practicalities
Mechanism of education and teaching: problem oriented, short introductions, case presentations, maybe involvement of real patients
Let's not duplicate existing courses
When inviting people asses first their basic knowledge by a simple questionnaire
Mix the experts with the teachers
Participants can bring their own cases
Begin with a summary and end with a summary(like the tv news)
For whom: all clinicians interested in IEM and that have already expierience.
Where: UMC Utrecht
How long: 2 full days, 4 sessions covering 8 diseases, like Wednesday noon till Friday 2pm
1,5 hour session, video, patient, discussion every 10-20 minutes.
1st training: PKU, Homocystinuria, X-ALD, Gaucher, Galactosemia, AKU
2nd meeting: Fabry, OTC, GSD I, GSD III, FAO, OA/MMA/GAI/IVA/PA, MPS

Format example of training**:**

Wednesday
Intro: 30 min

Session I PKU1
Session II PKU2, more practical, design a diet (computer) or debate: diet or none diet or each group in the session to make a cost benefic analysis to be or not to be on diet.

Take away massage: issues relating to diet in adulthood, long term complications, a diet for adults, manage pregnancy, issues around diet in adulthood, psychosocial issues, individual approach??? The systematic review, new treatment: BH4, the late diagnosed(never treated)
Maternal, outcome diet, contraception, preconception counseling, diet
1 speaker/facilitator(own group) and 2 to lead the discussion(from other group)

closing remarks: 15 min

Thursday:
Morning:
I HCt: clinical presentation, diagn, therapy, diet or no diet, targets,
Complications, pregnancy
II AKU: history, presentation, therapy, complications

Closing remarks/take home: 15 minutes

Lunch

Afternoon
Galactosemia: plenary session monitoring, diet, long term complicatios/outcome.
Fertility and puberty

Wrapping up 15 min

Dinner

Friday:
I X-ALD: clinical spectrum, diagn, assessments, neuropsycolo/neuropsyciolo…and therapy
II Gaucher: clinical spectrum, molecular etc assessments, therapy, enzyme and substrate aprivation. EMP

General session/feedback/evaluation etc

Action list
Zaira and Harold:
Exploration website possibilities (UMC U)
Make a cost analysis of the training
Inform about accreditation of the trainings (for this we need all national contact points from you)
Look for a European globe for the book cover
Make a flyer concept for publicity for the training
Contact publisher with several questions: scope, color of cover, costs, max pages etc
Send a reminder of the deadlines to every member

For every member:
Work on a draft review!

Timetable & deadlines
First draft review: 1st of June 2003-02-12
Harold and Zaira will do the first editing and circulate all papers to be reviewed by every member
Deadline for comment: 1st of Oktober
After this deadline every group will get their own review back.
1st of December: last version of review/chapter.
December/January/February: editing by Zaira and Harold
First announcement of training: SSIEM Brisbane
First training planned: may 2004
Second training oktober 2004
Meeting February 2003: 7-9 February 2003
First training session: june 2003: 5-8 june or 12-15 june
Second training session: octobre 2003

Comments about TEAM I
Too broad without precise endpoints
Te vrijblijvend
Goal not clear enough

Comments for TEAM II
Write a letter to the editor of BMJ and inform about the possibility for the ABC series.
Set a feasible endpoint/goal

Comments for 6Th Framework grant application
We need ideas for clinical trials

ALL REMARKS AND SUGGESTIONS ARE WELCOME!

I: Form and content of the hard-copy book

General Format of book:

Each topical chapter:

0: Biochemical pathway table

1. Introduction	disease pathophysiology clinical presentation essential diagnostics: 2 or 3 sentences
2. Therapy	diet or pharmacology or other targets and monitoring
3. Complications	frequently or rarely seen (table or text) treatment and monitoring of complications
4. Fertility issues	fertility, contraception and pregnancy (and outcome)
5. Psychosocial issues	quality of life, profession and so one
6. Summary	key messages, possible future developments, controversial issues, justification of sources

7. References for introduction use 1 or 2 reviews or books, further a list of the main papers (format: reference manager)

Release: September 2004

J: Form and content of the training session

General form and content
Maximum of 25 participants
Target group: clinicians interested in inborn errors of metabolism and who have already expierience.

Training is about the practicalities of using current, reliable knowledge and implementing care Two different training sessions
Mechanisms of education and teaching: Mechanisms of education and teaching: problem oriented, short introductions, case presentations, involvement of real patients. Participants can bring their own cases
When inviting participants: first assess their basic knowledge by a simple questionnaire
Mix experts with the teachers
Begin with a summary and end with a summary (like the TV news)
Where: University Medical Centre, Utrecht, the Netherlands
How long: 2 full days, 4 sessions covering 8 diseases, Wednesday noon till Friday 2 pm. Each session: 1,5 hours, includong video, patient presentation, discussion every 20 minutes.
When: first training: May 2004, Second training: oktober 2004.
Content of the training session:
First training:
Phenylketonuria, homocystinuria, X-linked adrenoleukodystrophia, galactosaemia, alkaptonuria
Second training: Fabry, ornithine transcarbamylase deficiency, Glycogen storage diseases I and III, fatty acid oxidation disorders, organic acidurias, lysosomal storage disorders

Format first training**:**

Wednesday

Afternoon

Introduction: 30 min

Session I:
PKU1

Session II:
PKU2, more practical, design a diet (computer) or debate: diet or none diet or each group in the session to make a cost benefic analysis to be or not to be on diet.

Take away massage: issues relating to diet in adulthood, long term complications, a diet for adults, manage pregnancy, issues around diet in adulthood, psychosocial issues, individual approach? The systematic review, new treatment: BH4, the late diagnosed(never treated)
Maternal, outcome diet, contraception, preconception counseling, diet
1 speaker/facilitator(own group) and 2 to lead the discussion(from other group)

Closing remarks: 15 min

Thursday

Morning:
Session I:
Homocystinuria: clinical presentation, diagn, therapy, diet or no diet, targets,
complications, pregnancy

Session II:
Alkaptonuria: history, presentation, therapy, complications

Closing remarks/take home: 15 minutes

Lunch

Afternoon

Galactosemia: plenary session; monitoring, diet, long term complications and outcome; fertility and puberty
wrapping up 15 min

Dinner

Friday

Session I:
X-ALD: clinical spectrum, diagn, assessments, neuropsycological outcome , therapy therapy

Session II:
Gaucher: clinical spectrum, molecular etc assessments, therapy,
enzyme and substrate aprivation. EMP

General session Summing up, feedback and evaluation

K: Example of review

REVIEW ON PROPIONIC ACIDEMIA

Celia Pérez-Cerdá, Begoña Merinero, Magdalena Ugarte

Centro de Diagnóstico de Enfermedades Moleculares. Dpto de Biología Molecular. Facultad de Ciencias. Universidad Autónoma de Madrid. Cantoblanco 28049Madrid, Spain.
e.mail:cpcerda@cbm.uam.es

Introduction

Propionic acidemia (PA; MIM 606054) is one of the most frequent organic aciduria involving the catabolism of branched- chain amino acid metabolism. It is caused by the inherited deficiency of the mitochondrial biotin-dependent enzyme propionyl-CoA carboxylase (PCC; E.C.6.4.1.3), that catalyses the conversion of propionyl-CoA to D-methylmalonyl CoA, the major degradation pathway of propionyl-CoA formed by the catabolism of the essential amino acids threonine, methionine, valine and isoleucine, odd-chain fatty acids and cholesterol or gut bacteria (see figure 1). Native PCC is a heteropolymeric mitochondrial enzyme, composed by two types of subunits, α and β, in a proposed $\alpha_6\beta_6$ configuration, with the α-subunit containing the covalently attached biotin prosthetic group (Fenton et al. 2001).

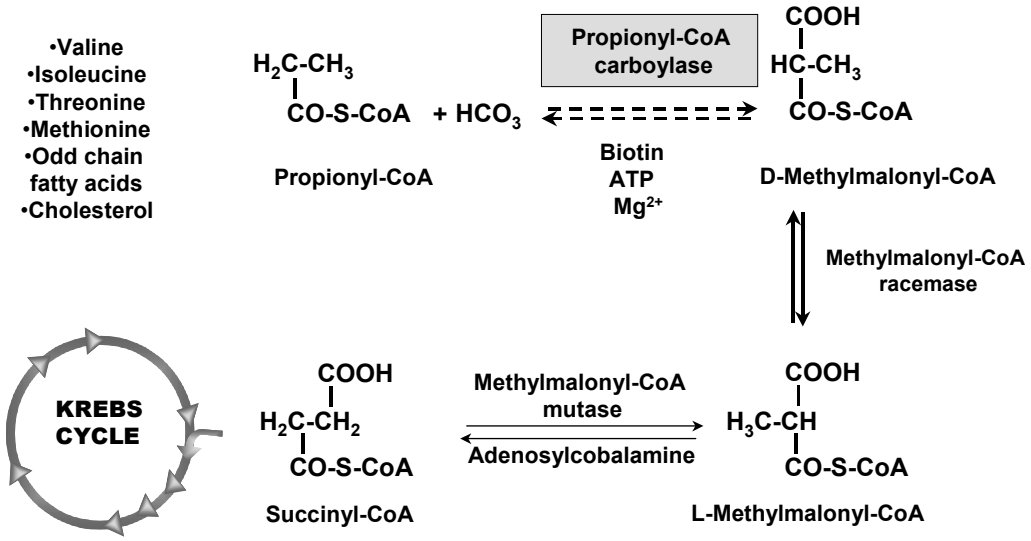

Figure 1

Genetics

PA is an autosomal recessive disorder with an incidence of around 1 in 100.00 (Chace et al. 2001). Complementation analysis of cultured fibroblasts from PA patient has revealed two main intergenic complementation groups: pccA resulting from mutations
in the α (PCCA) gene (MIM 232000), and pccBC resulting from mutations in the β (PCCB) gene (MIM 232050). The cDNAs from α and β subunits have been cloned and the corresponding nuclear genes PCCA and PCCB have been mapped to chromosomes 13q32 (Lamhonwah et al. 1986) and 3q13.3-q22 (Kraus et al. 1986; Lamhonwah et al. 1986), respectively (see figure 2). Genomic structure of both *PCCA* (Campeau et al. 2001) and *PCCB* genes (Rodríguez-Pombo et al. 1998) are available and up to date, over 60 mutations have been reported causing PA (Ugarte et al 1999, Campeau et al 1999; Muro et al 1999 Ravn et al 2000 Pérez et al 2003). Several works have been performed in order to elucidate the functional effect of mutations on enzyme structure and/or function and their relationship to disease phenotype (Chloupkova et al 2000, Chloupkova et al 2002, Clavero et al, 2002, Pérez-Cerdá et al 2003).

Clinical picture

Many PA patients manifest in the early weeks of life (early onset). They exhibit clinical signs of the intoxication-type disease with ketoacidosis and/or hyperammonemia. Usually, after an initial symptom-free period of a full-term baby born after a normal pregnancy and delivery, first signs are feeding difficulties, vomiting, somnolence and/or coma, hypotonia and abnormal movements as myoclonic jerks and convulsions. Less severe cases may present in infancy or even later during childhood (late onset). Clinical manifestations in these patients are more insidious and usually related to infections or with mainly gastrointestinal symptoms. Moreover, propionic acidemia may present first with prominent neurological disease without acute episodes of massive ketoacidosis and hyperammonemia (Ozand et al. 1994, Nyhan et al, 1999). Asymptomatic patients have been reported (Wolf et al. 1979, Kuhara et al 1988)

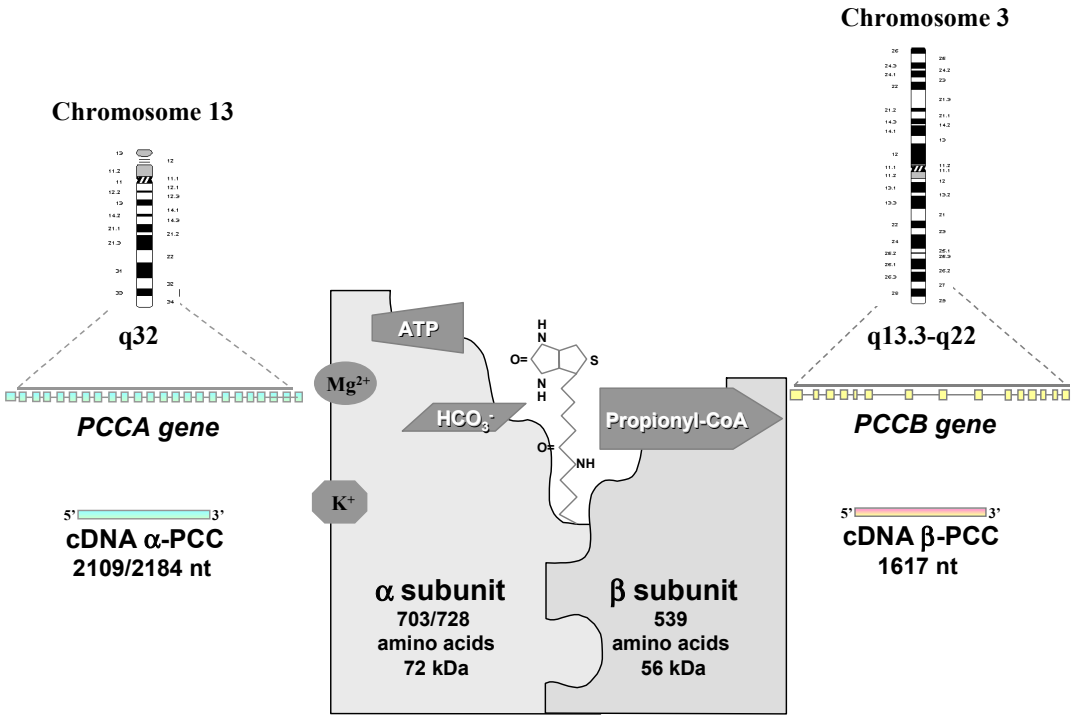

Figure 2

Metabolic derangement

PA is characterized by greatly increased concentrations of propionic acid derived from hydrolysis of propionyl-CoA in blood and urine. The accumulated propionyl-CoA goes to alternative pathways leading to the formation of number metabolites, mainly organic acids which are also found in large amount in fisiological fluids: 3-OH-propionate, methylcitrate, propionyl-glycine. During ketotic episodes, 3-OH butyrate, 3-OH-isovalerate, 3-OH-n valerate, 3-keto-n-valerate, and other intermediates of isoleucine catabolic pathway such tiglic acid, tiglylglycine and 2-methyl-3-OH butyrate can be also found. Moreover, the presence of high levels of propionyl-CoA in the cell result in the inhibition of the N-acetyl glutamate synthetase and of the glycine cleavage system explaining the hyperammonemia and hyperglycinemia reported in PA patients. Because of the activity of carnitine-N-acylase, patients have increased plasma concentration of propionyl-carnitine and a relative secondary carnitine deficiency (Chalmers et al. 1984). Furthermore, propionyl-CoA can act as the primer in place of acetyl-CoA during the novo fatty acid synthesis resulting in the formation of odd-numbered fatty acids (OLCFA), which can be incorporated into lipids throughout pre- and post-natal life (Wendel et al. 1991).

Diagnostic tests

The diagnosis of PA is usually based on the detection and quantification of urinary 3-OH-propionate and methylcitrate, the major diagnostic metabolites, by GC-MS. Frequently, patients also showed hyperammonemia, hyperglycinemia and hypocarnitinemia.

Tandem mass spectrometry (MS/MS) analysis of propionyl-carnitine in filter-paper blood specimens is used as a newborn screening assay in order to identify pre-symptomatic PA infants (Naylor and Chace 1999). Confirmation of diagnosis is done by PCC determination in lymphocytes or cultured fibroblasts that usually shows a severe reduction (1-5%) and by DNA analysis. Reliable prenatal studies can be done during the first trimester of gestation based on metabolites determination in amniotic fluid (Jakobs et al. 1990; Shigematsu et al. 1996), direct enzyme assay (Perez-Cerda et al. 1989; Rolland et al. 1990) and molecular studies in intact or cultured chorionic villi (Muro et al. 1999).

Differential diagnosis must be done from sepsis, birth trauma, gastrointestinal obstruction and cardiorespiratory difficulties as well as from other ketoacidotic or hyperammonemic conditions including severe dehydration, diabetes mellitus, Reye syndrome, glycogenosis, urea cycle disorders and several others organic acidemia, particularly from multiple carboxylase deficiency.

Treatment and monitoring

The goal of the dietary treatment for PA is to reduce the propionate production and to facilitate the removal of toxic metabolites. Several isotope stable studies have estimated that approximately 50% of propionate production is derived from amino acids, 20% from the gut and 30% from the catabolism of odd-chain fatty acids (Thompson et al. 1990b).

Dietary treatment is based on:

Restriction of natural protein (0.5-1.5 g/kg/day) with added supplemental protein mixture free of precursors amino acids (threonine, methionine, valine and isoleucine) to meet the recommended daily allowance.

Administration of carnitine (100-200 mg/kg/day) to remove propionyl-CoA groups by enhancing urinary excretion (Roe et al. 1984) and to prevent carnitine deficiency.

Administration of metronidazole (10-20 mg/kg/day) to reduce propionate production from flora bowel (Thompson et al. 1990a).

Sometimes Isoleucine (200mg/day) is also supplemented to prevent cutaneous problems.

Prolonged fasting should be avoided in order to prevent catabolism and thus lipolysis that causes an increase of propionate production from odd-chain fatty acids oxidation (Thompson and Chalmers 1990). In this sense, nasogastric tube or gastrostomy is valuable to prevent endogenous protein and lipid catabolism. Sufficient supply of energy intake, vitamins and minerals must to be administrated to prevent nutritional complications (Yannicelli et al. 1992, Matern et al 1996)

To date, a small number of PA patients have been liver transplanted. When there are no major post-operative complications, patients can return to normal diet but metabolic abnormality is only partially corrected (Schlenzig et al. 1995, Saudubray et al 1999, Yorifuji et al, 2000).

The correction of PCC deficiency by gene transfer in skin fibroblasts of PA patients may have important implications for somatic gene therapy (Lamhonwah et al. 1994; Stankovics and Ledley 1993, Pérez-Cerdá et al. 2002). A mouse model of PA has been created and a liver-specific PCC supplementation via a transgene has been proposed as a potential mode of treatment of human PA (Miyazaki et al. 2001).

For monitoring the metabolic status, urinary organic acids and ketone bodies, and plasma ammonia, amino acids, and OLCFA (Sperl et al. 2000) should be regularly controlled.

Outcome and prognosis

Several reports describing the outcome and long-term management of patient with PA has been reported (Lehnert et al. 1994; Leonard 1995, van der Meer et al 1996). On the whole, PA is a severe disorder with a high rate of mortality (40%) and a high incidence of mental retardation and neurological complications among survivors. There is not correlation between clinical phenotype, degree of PCC deficiency in fibroblasts and the affected gene, since the proportion of deaths and retardations is similar in both molecular groups (PCCA- or PCCB-deficient patients) (Pérez-Cerdá et al. 2000).

Long-term complications
Neurologic complications such as mental retardation and movement disorders (choreoatetosis and dystonia) (Surtees et al. 1992), basal ganglia involvement (Harding et al. 1991, Hamilton et al 1995, Haas et al 1995, Bergman et al 1996, Pérez-Cerdá et al 1998, Al-Essa et al 1999, Burlina et al 2001), dysautonomia (Harris et al. 1980), acute hemiplegia (Shigematsu et al. 1990), spastic cuadriparesis (Przyrembel et al. 1979, Nyhan et al 1999) and dementia (Sethi et al 1989) have been extensively reported. Cerebelar hemorrhage complicating the neurologic course of PA has been also described (Dave et al. 1984).
Other complications include: failure to thrive, particularly in height (van der Meer et al. 1996), pancytopenia (Stork et al. 1986), immunodeficiency (Raby et al. 1994) and recurrent infections (Al Essa et al. 1998), acute pancreatitis: (Kahler et al. 1994, Burlina et al 1995), cutaneous manifestations (Bodemer et al. 1994), retarded puberal development (Pérez-Cerdá et al. 2000), osteoporosis (Lehnert et al. 1994) and cardiomyopathy (Massoud and Leonard 1993, Collins et al 1994).

Specifics items
Pregnancy: To date, there is only one case report of pregnancy in a woman with mild form of PA. A protein-restricted diet with carnitine supplementation was employed to manage the pregnancy and a healthy girl was delivered without maternal metabolic descompensation (Van Calcar et al. 1992)
Anaesthesia: Anaesthetic management for PA is widely described (Harker et al. 2000)

Reports of adult patients (> 15y)
(Gebarski et al, 1983) (Thompson et al 1990) (Thompson et al. 1990a) (Van Calcar et al. 1992) (Surtees et al. 1992) (Sbai et al. 1994) (van der Meer et al. 1996) (Nyhan et al. 1999) (Pérez-Cerdá et al. 2000) (Burlina et al. 2001)

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