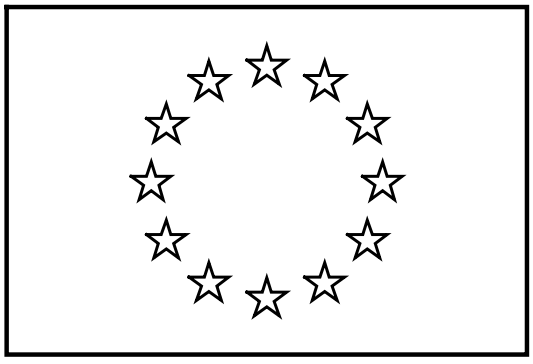
Programme of community action on rare diseases

Contract n° 2000/CVG4-808

ORPHANET : Final scientific report

February 2002



Summary

The project was to extend the content of the already existing ORPHANET database which was exclusively a French project from 1997 until 2000, to build up a truly European database. The first year was the feasibility study year and a pilot study with a few countries (4).
The European project had two parts: 1) the establishment of an on-line Encyclopaedia on rare diseases, 2) the extension of the existing database of services to other European countries.

For the encyclopaedia, the board of editors was established progressively, speciality by speciality and authors of texts nominated. The number of authors who have already written up one or more entries is 116, out of 428 who have accepted so far. For the 3,500 diseases, there are on-line: 899 summaries in French, 731 summaries in English, 327 review articles in French and 116 review articles in English.

The new European version of the website was launched on October 15, 2001. This is a true new version, with a new graphic chart and the possibility to query in six languages. The general information about rare diseases and orphan drugs in general has been dramatically expended.

The partners were trained to use our methodology through visits, e-mails and phone calls. All the partners have identified their sources of information. The data about services are partially collected in the four new countries and updated for France. All the thesaurus were translated into Italian and German as well as the screens. The number of names of diseases with their synonyms to be translated was over 6,000.

A quality charter was defined by the partners and agreed on.

The usefulness of the database was assessed through the number of connections. In November 2001, we have had during the month 44.425 visits from 30.428 different sites from 94 different countries. The average number of pages read was 10 per visit. In addition we received an average of 65 unsollicited e-mails from patients or professionals. A methodology to handle ethically these messages was developped.

As a project leader of Orphanet, Ségolène Aymé was invited 21 times within the first year of the contract to give a lecture on Orphanet. These invitations came from the Academia, the Industry and from Agencies and took place in five different European countries.

The Orphanet project is developing according to the plans. The first year was a very busy one which permitted to explore all the difficulties for transmitting our five-year experience with data collection. The procedures are now well in place and should be easily adopted by the new partners. The experience also clearly showed to the partners that there was a great need in getting national funding to expand the local teams. Several countries are on the way of having complementary funding at the governmental level.

List of partners

Subject : **ORPHANET**

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GENERAL REPORT

I.1 Goal of the EC funded project

The project was to extend the content of the already existing ORPHANET database which was exclusively a French project from 1997 until 2000, to build up a truly European database. The first year was the feasibility study year and a pilot study with a few countries (4). It was planned to test:

- the robustness of the database in the configuration of multiple independent teams collecting and entering data from remote sites
- the feasibility of the collaboration with professional organizations
- the real cost of the editorial secretariat

The European project has two parts: 1) the establishment of an on-line Encyclopaedia on rare diseases, 2) the extension of the existing database of services to other European countries.

I.2 The on-line Encyclopaedia

The initial goal was:

- to establish the European editorial board
- to nominate potential authors for 1,000 diseases
- to obtain 300 new texts
- to evaluate the cost of the editorial office
- to test the feasibility of the translation into other European languages, starting with French, German and Italian and its cost

The first step was to hire one editor (1 January 2001) and one assistant editor (1 April 2001) in Paris. They established the board of European editors by re-contacting all the experts who had accepted to join the project and defining with them their area of responsibility.

I.2.1 The current board of editors

The board of editors was established progressively, speciality by speciality. It is currently the following:

CARDIOLOGY
Pr Duboc, Paris, France
Dr Melacini, Padova, Italy
Pr McKenna, London, UK
Pr Nigro, Napoli, Italy
CYTOGENETICS
Pr Forabosco, Modena, Italy
Pr Petersen, Athens, Greece
Pr Pignatti, Verona, Italy
Pr Tommerup, Copenhagen, Denmark
Pr Vekemans, Paris, France

DERMATOLOGY
Pr Blanchet-Bardon, Paris, France
Pr Caputo, Milan Italy
Pr Eady, London, United Kingdom
Pr Happle, Marburg, Germany
Pr Mascaro, Barcelona, Spain
Pr van Vloten, Utrecht, Netherlands

DYSMORPHOLOGY
Dr Clayton-Smith, United Kingdom
Dr Cormier-Daire, Paris, France
Dr Devriendt, Belgium
Dr Gonzalez, Paris, France
Pr Hennekam, Amsterdam, Netherlands
Pr Lacombe, Bordeaux, France
Pr Verloes, Liège, Belgium

ENDOCRINOLOGY
Pr Bouchard, France

GASTROENTEROLOGY
Pr Chayvialle, Lyon, France
Pr Jansen, Groningen, Netherlands
Pr Porro, Milano, Italy
Pr Rösch, Frankfurt/Main, Germany

GENETICS
Pr Dallapiccola, Rome, Italy
Pr Goossens, Creteil, France
Pr Karlsson, Lund, Sweden
Dr Muller, Wuerzburg, Germany
Pr Schmidtke, Germany

HEMATOLOGY
Pr Casadevall, France

HEPATOLOGY
Pr Erlinger, Clichy, France
Pr Reichen, Bern, Germany

IMMUNOLOGY
Pr Fischer, Paris ,France
Pr Notarangelo, Brescia, Italy

INFECTIOUS DISEASES
Pr Caramello, Turin, Italy
Pr Carbon, Paris, France

Pr Danis, Paris, France
Pr Feldmeier, Berlin, Germany
Pr Hommel, Liverpool, UK
Pr Lew, Geneva, Switzerland
Pr Lode, Berlin, Germany
Pr van der Meer, Nijmegen, Netherlands

INFECTIOUS FOETO/EMBRYOPATHIES
Pr Catherine Peckham, London, UK

INTERNAL MEDICINE/ RHEUMATOLOGY
Pr Bombardieri, Pise, Italy
Pr Delmas, Lyon, France
Pr Devogelaer, Brussels, Belgium
Dr Font, Barcelona, Spain
Pr Guillevin, Paris, France ;
Pr Mariette, Paris, France
Dr Moutsopoulos, Athena, Greece
Pr Papapoulos, Leiden, Netherlands
Pr Rizzoli, Geneva, Switzerland

PRIONS DISEASES
Pr Alpérovitch, France

METABOLIC DISEASES
Pr Bachman, Lausanne, Switzerland
Pr Baumann, Paris, France
Pr Federico, Sienna, Italy
Pr Leonard, London, United Kingdom
Pr Saudubray, Paris, France
Pr van den Berghe, Bruxelles, Belgium
Pr Wendel, Dusseldorf, Germany

NEPHROLOGY
Pr Grunfeld , Paris , France
Pr Haycock , London, United Kingdom
Pr Holzer, Graz, Austria
Pr Niaudet, Paris, France
Pr Scolari, Brescia, Italy
Pr Sessa, Vimercate, Italy
Pr Torra, Barcelone, Spain

NEUROLOGY
Pr Brice, Paris, France
Pr Edström, Stockholm, Sweden
Pr Landwehrmeyer, Freibourg, Germany
Dr Taroni, Milan, Italy

Pr de Visser, Amsterdam, Netherlands
Pr Wood, London, United Kingdom

NEUROMUSCULAR DISORDERS
Dr Bonnemann, Göttigen, Germany
Pr Merlini, Bologna, Italy
Pr Muntoni, London, United Kingdom
Dr Padberg, Nijmegen, the Netherlands
Dr Urtizberea, Paris, France
Dr Wallgren, Helsinki, Finlande*

NEUROPEDIATRIC DISEASES
Pr Campos-Castello, Barcelone, Spain
Pr Guzzetta, Roma, Italy
Pr Ponsot, Paris, France
Pr Szliwowski, Bruxelles, Belgium

ONCOLOGY
Pr de Kraker, Amsterdam, Netherlands
Pr Fernandez-Delgado, Valencia, Spain
Pr Perilongo, Padova, Italy
Pr Philip, Lyon, France
Pr Pinkerton, Sutton, United Kingdom
Pr Stevens, Birmingham, United Kingdom
Pr Symann, Bruxelles, Belgium
Pr Vassal, Villejuif, France

OPHTALMOLOGY
Pr Bird, London, UK
Dr Dufier, Paris, France
Pr Gaudric, Paris, France
Pr de Jong, Amsterdam, Netherlands
Pr de Laey, Gent, Belgium
Pr Leys, Leuven, Belgium
Pr Marshall, London, UK
Pr Marsili, Milano, Italy
Pr Mayer, Erlangen, Germany

OTOLARYNGOLOGY
Pr Anniko, Sweden
Pr Martini, Ferrara, Italy
Pr Sterkers, Paris, France
Pr van de Heyning, Antwerp, Belgium

PEDIATRIC CARDIOLOGY
Pr Anderson, London, United Kingdom
Dr Bonnet, Paris, France

Pr Deanfield, London, United Kingdom
Dr Marino, Roma, Italy
Dr Parsons, Leeds, United Kingdom

PEDIATRICS SURGERY
Pr Bargy, Paris, France
Dr Tovar, Madrid, Spain
Pr Sokal, Brussels, Belgium*
Dr Kluth, Hamburg, Germany*

PHARMACY
Dr Juarez, Spain
Dr Nunn, United Kingdom.
Dr Rieutord, Paris, France**.**

PNEUMOLOGY
Pr du Bois, London, United Kingdom
Pr Cordier, Lyon, France
Pr Costabel, Essen, Germany
Dr Lazor, Geneva, Switzerland

PEDIATRICS RHEUMATOLOGY
Pr Dressler, Hannover, Germany.
Pr Martini, Pavia, Italy
Dr Prieur, Paris, France
Pr Southwood, Birmingham, United Kingdom
Pr Woo, London, United Kingdom

TERATOLOGY
Dr Arnon, Jerusalem, Israel
Dr Garbis, Leiden, the Netherlands
Dr Robert, Lyon, France
Dr Schaeffer, Berlin, Germany

TOXICOLOGY
Pr Baud, Paris, France
Pr Hantson, Brussells, Belgium
Dr Manzo, Pavia, Italy
Dr Bateman, Edinburgh, United Kingdom

I.2.2 The editorial process/methodology

Each editor was asked to select a number of diseases for which he/she would be responsible for. The Orphanet team had to manage the delicate issue of several editors selecting the same diseases and of the other diseases not selected by any one.
The editors were then asked to nominate potential authors for the entries they were in charge of. The authors were then contacted, their answers managed and their work followed-up.

A set of summaries was sent to professional Italian translators (from French into Italian). The quality of the translation was then evaluated by Italian experts.
The translation from English to French was performed at the editorial office level. The translation from French to English was performed by a professional scientific translator.

I.2.3 The outcome

The list of authors who have already written up one or more entries is the following: (the date indicates the date this text was put on-line). In total 116 review articles in English were produced as a result of the current contract. This is a very satisfactory outcome as the maximum one editor can achieve within one year is 70-80 texts.

Name of disease	Author	Date
2,8 dihydroxyadenine urolithiasis	SIMMONDS	23/07/01
3c syndrome	FAIVRE	23/07/01
4-hydroxybutyricaciduria	JAEKEN	29/08/01
5-oxoprolinase deficiency	RISTOFF	22/05/01
6-pyruvoyl-tetrahydropterin synthase, deficiency	DHONDT	18/04/01
Achondrogenesis	FAIVRE	23/07/01
Acromesomelic dysplasia hunter thompson type	FAIVRE	24/07/01
Acromesomelic dysplasia, Grebe type	FAIVRE	24/07/01
Acromesomelic dysplasia, Maroteaux type	FAIVRE	24/07/01
Adenosine monophosphate deaminase deficiency	GROSS	26/09/01
Adrenoleukodystrophy, X-linked	AUBOURG	02/03/01
Agammaglobulinemia, autosomal recessive	DURANDY	21/03/01
Alexander disease	RODRIGUEZ	31/08/01
Allan-Herndon syndrome	SCHWARTZ	09/05/01
Alport syndrome	SESSA	23/04/01
Angioneurotic edema	BOUILLET-CLAVEYROLAS	10/04/01
Ankylosing spondylarthritis	DOUGADOS	26/11/01
Antiphospholipid syndrome	TEKTONIDOU	16/11/01
Antisynthetase syndrome	TZIOUFAS	16/11/01
Autoimmune lymphoproliferative syndrome	LE DEIST	21/03/01
Bartter syndrome	COLUSSI	04/09/01
Beckwith-Wiedemann syndrome	GICQUEL	24/09/01
Behcet syndrome	WECHSLER	24/09/01
Berger disease	SAVOLDI	28/06/01
Betaketothiolase deficiency	FUKAO	21/09/01
Bethlem myopathy	URTIZBEREA	03/10/01

Bullous pemphigoid	BERNARD	25/06/01
CACH syndrome	RODRIGUEZ	31/08/01
Caffey disease	HALL	18/09/01
Carnitine-acylcarnitine translocase deficiency	BRIVET	19/04/01
Carnosinemia	JAEKEN	29/08/01
Castleman disease	SARROT-REYNAULD	28/08/01
CDG syndrome	SETA	22/02/01
Celiac disease	HOLTMEIER	02/03/01
Centrotemporal epilepsy	PRATS-VINAS	19/04/01
Cluster headache	VISY	05/04/01
Coffin-Lowry syndrome	HANAUER	13/09/01
Cogan syndrome	VINCENEUX	24/07/01
Congenital nephrotic syndrome, finnish type	NIAUDET	18/10/01
Continuous spike-wave during slow sleep syndrome	METZ-LUTZ	06/06/01
Corpus callosum agenesis	MOUTARD	18/06/01
Creatine deficiency, cerebral	STOECKLER-IPSIROGLU	23/03/01
Crigler-Najjar syndrome	LABRUNE	27/11/01
Crohn disease	CORTOT	27/09/01
Cystinosis	NIAUDET	04/10/01
Dehydratase deficiency	DHONDT	18/04/01
Deletion 2q24	MAAS	23/07/01
Denys-Drash syndrome	NIAUDET	17/10/01
Desbuquois syndrome	FAIVRE	24/07/01
Diffuse leiomyomatosis with Alport syndrome	SESSA	23/04/01
Dihydropteridine reductase deficiency	DHONDT	18/04/01
Dubowitz syndrome	TSUKAHARA	25/06/01
FG syndrome	OPITZ	13/09/01
Fibrochondrogenesis	AL-GAZALI	27/03/01
Fibrodysplasia ossificans progressiva	URTIZBEREA	03/10/01
Gamma-glutamyl transpeptidase deficiency	RISTOFF	22/05/01
Gamma-glutamylcysteine synthetase deficiency	RISTOFF	22/05/01
Genetic susceptibility to infections caused by BCG and atypical mycobacteria	CASANOVA	21/03/01
Gitelman syndrome	KNOERS	21/11/01
Glutaryl-CoA dehydrogenase deficiency	HOFFMANN	22/06/01
Glycogen storage disease type 2 B	FROISSART	16/01/02
Gorlin syndrome	LO MUZIO	16/01/02
Griscelli disease	DE SAINT-BASILE	21/03/01
GTP cyclohydrolase	DHONDT	18/04/01

deficiency		
Hereditary primary hypomagnesemia (generic term)	KNOERS	20/11/01
Homocarnosinosis	JAEKEN	29/08/01
Hyper-IGM syndrome, autosomal recessive	DURANDY	21/03/01
Hyperinsulinism in children, congenital	DE LONLAY	03/04/01
Hyperoxaluria	NIAUDET	19/10/01
Hypomagnesemia hypercalciuria, familial	KNOERS	20/11/01
Hypomagnesemia with hypocalciuria	KNOERS	21/11/01
Kawasaki disease	MAHR	28/06/01
Kimura disease	LARROCHE	28/08/01
Langerhans cell histiocytosis	DONADIEU	21/06/01
Lesch-Nyhan syndrome	TORRES JIMÉNEZ	05/09/01
Lipodystrophy, Berardinelli type	VAN MALDERGEM	19/11/01
Macrophagic myofasciitis	CHERIN	31/08/01
Maternal hyperphenylalaninemia	ABADIE	01/10/01
Mediterranean fever, familial	TOUITOU	28/08/01
Medullary cystic kydney disease, autosomal dominant	AMOROSO	28/06/01
Megalencephalic leukodystrophy	LOPEZ-TERRADAS	20/04/01
Menkes syndrome	CORDIER-ALEX	09/03/01
Mesangial sclerosis, diffuse	NIAUDET	10/10/01
Mucopolysaccharidosis type 1	BECK	05/09/01
Nail patella syndrome	NIAUDET	04/10/01
Nance Horan syndrome	TOUTAIN	10/01/02
Nephronophtisis	NIAUDET	19/10/01
Nephropathy familial with gout	GHIGGERI	28/06/01
Non-alcoholic steatohepatitis	DUFOUR	03/02/01
Oculopharyngeal muscular dystrophy	URTIZBEREA	12/06/01
Oligomeganephronic renal hypoplasia	NIAUDET	03/10/01
Orofaciodigital syndrome type1	PRATI	14/06/01
Phosphoribosylpyrophosphate synthetase superactivity	BECKER	22/07/01
Polycystic kidney disease, dominant type in childhood	NIAUDET	18/10/01
Polycystic kidney disease, recessive type	NIAUDET	19/10/01
Progeria	FAIVRE	24/07/01
Prolidase deficiency	JAEKEN	28/08/01
Pyomyositis	LORTHOLARY	26/11/01

Pyroglutamicaciduria	RISTOFF	23/05/01
Relapsing polychondritis	DROSOS	09/11/01
Sarcosinemia	JAEKEN	29/08/01
Scleroderma	VLACHOYIANNOPOULOS	05/11/01
Seckel syndrome	FAIVRE	24/07/01
Severe combined immunodeficiency due to JAK3 (Janus Kinase 3) deficiency	NOTARANGELO	06/11/01
Severe combined immunodeficiency, alymphocytotic type	FISCHER	02/04/01
Sjögren syndrome	MANOUSSAKIS	08/11/01
Spondyloepimetaphyseal dysplasia	HALL	19/09/01
Succinyl-CoA acetoacetate transferase deficiency	FUKAO	21/09/01
Transcobalamin II deficiency	KAMOUN	11/06/01
Triose phosphate-isomerase deficiency	LIVET	26/06/01
Vitamin resistant rickets	GARABEDIAN	21/01/02
Whipple disease	FEURLE	02/03/01
Wiskott-Aldrich syndrome	FISCHER	02/04/01
Xanthinuria	SIMMONDS	23/07/01
X-linked severe combined immunodeficiency	DE SAINT-BASILE	16/11/01
ZAP70 deficiency	NOTARANGELO	07/11/01

In addition to these review articles, the authors were also asked to write up summaries for diseases where a long review article was not necessary. The list of the 44 summaries already available is the following:

Name of disease	**Author**	**Date**
Acrocephalopolydactyly	NAEYAERT	20/04/01
African trypanosomiasis	PARIS	06/12/01
Arrythmogenic right ventricular dysplasia (ARVD)	FONTAINE	19/02/01
Aspergillosis	DATRY	28/11/01
Borjeson-Forssman-Lehmann syndrome	MORAINE	27/11/01
Cerebelloparenchymal disorder 3	MÉGARBANE	16/05/01
Chronic berylliosis	PROST	28/11/01
Chronic hiccup	CABANE	16/11/01
Cryptococcosis	DATRY	28/11/01

Cryptosporidiosis	DATRY	28/11/01
Dent disease	GRUNFELD	27/11/01
Distal myopathy with vocal cord weakness	PENISSON-BESNIER	29/11/01
Distal myopathy, Nonaka type	PENISSON-BESNIER	29/11/01
Epidermolysa bullosa simplex and limb girdle muscular dystrophy	URTIZBEREA	03/10/01
Familial focal segmental glomerulosclerosis	GRUNFELD	27/11/01
Familial hemophagocytic lymphohistiocytosis (FHL)	DE SAINT-BASILE	16/11/01
Fetal hydantoin syndrome	ROBERT-GNANSIA	19/11/01
Fetal valproic syndrome	ROBERT-GNANSIA	19/11/01
Giant cell arteritis	DUHAUT	13/12/01
Hereditary methemoglobinemia, recessive	BEAUVAIS	29/11/01
Hyperferritinemia, hereditary, with congenital cataracts	BEAUMONT	20/11/01
Hypomagnesemia caused by selective magnesium malabsorption	KNOERS	28/11/01
Hypomagnesemia with normocalciuria	KNOERS	21/11/01
Hypoparathyroidism, deafness and renal disease (HDR)	GRUNFELD	27/11/01
Johanson blizzard syndrome	STEINBACH	17/05/01
Microsporidiosis	DATRY	28/11/01
Murcs association	CARRANZA-LIRA	15/03/01
Mycetoma	DATRY	28/11/01
Nephrotic syndrome, idiopathic steroid-resistant	NIAUDET	19/10/01
Neuroectodermal melanolysosomal disease	NAEYAERT	24/04/01
Optic atrophy, Leber type	REYNIER	16/11/01

Optic nerve coloboma with renal disease	GRUNFELD	27/11/01
Phenobarbital embryopathy	ROBERT-GNANSIA	19/11/01
Plasminogen activitor inhibitor type 1 deficiency, congenital	ANGLES-CANO	16/11/01
Pseudohypoaldosteronism type 1	GRUNFELD	27/11/01
Schinzel-Giedion midface retraction syndrome	LABRUNE	27/11/01
Spontaneous periodic hypothermia	HAUSFATER	29/11/01
Tricuspid atresia	SIDI	27/11/01
Tuberous sclerosis	WOLKENSTEIN	16/11/01
Udd tibial myopathy	PENISSON-BESNIER	29/11/01
Uhl anomaly	FONTAINE	19/02/01
Waardenburg-Shah syndrome	TOURAINE	29/11/01
Welander distal myopathy, swedish type	PENISSON-BESNIER	29/11/01
Willebrand disease	MEYER	27/11/01

For the diseases where French summaries already existed, these summaries were translated into English. Therefore, the content of the ORPHANET encyclopaedia as of 1 December 2001 is:

Number of diseases:	3 500
Number of summaries in French	899
Number of summaries in English	731
Number of long texts in French	327
Number of long texts in English	116

I.2.4 Overall assessment of the Encyclopaedia project

Establish the European editorial board: this task has been completed for all specialties, except Oncology, Dermatology, Neurology and Ophthalmology. For these last four specialities, discussions are still going on the subset of diseases attributed to each editor and on the authors to be nominated.

Nomination of potential authors for 1,000 diseases: We obtained nominations of authors for 428 diseases in the six months following the final establishment of the editorial board for all specialities but four. Our process was very efficient, taking into consideration the fact that the editorial board members are very busy experts who are not compensated for their work for Orphanet.

Production of 300 new texts: 116 new texts were written directly in English by international authors. This is on line with the plans considering that it took 6 months to establish the authors database.

Evaluate the cost of the editorial office: Based on the experience of the past year, it is now estimated that one editor cannot process more than 70 review articles per year (creation and update) plus 50 additional summaries (creation and update) or process 200 summaries. This means that decisions have to be taken on how to set priorities. The current editorial team is composed of three editors. To manage a total of 1,200 diseases, which is the number of often requested diseases, ten editors would be needed to ensure a yearly update. In addition to the editorial work, the texts have to be put at the HTML format and then put on-line. This requires at least one full time webmaster, a position which is not filled in at the present time. The other 2,300 diseases would be documented by a few lines definition, not more. If the 3,500 diseases had to be documented, there would be a need for an editorial board of 15 people and 3 webmasters.

Test the feasibility of the translation in other European languages, starting with French, German and Italian and its cost: The translation from English to French and from French to Italian was tested using two different approaches. The translation English-French was done by an in-house editor with a university background in biology and in translation. The translations were then evaluated by an expert (S. Aymé). Only minor mistakes were observed, not modifying the information to deliver. The translation from French into English was done by a professional translator, specialized in Medicine and Biology. The results were very satisfactory but a few terms used were not the most appropriate one according to scientific standards. The translation from French into Italian was done through a partnership with the University of Genova in Italy, department of foreign languages. The translators were students. The quality of the translations were checked by an expert (B. Dallapiccola). He had to modify slightly all the texts. Translation by a professional has a high cost, around 1.2 Euro per word. Initially we planned to translate all the summaries. As a summary has an average number of 200 words, the cost per summary and per language is 240 Euro which means 240.000 Euro per language for 1,000 summaries. The current budget is not at all designed to face such expenses. It is even arguable whether the translation approach is the best one. A workshop to discuss this issue is planned in 2002 with all the partners.

I.3 The database of services

I.3.1 Goal of the sub-project

For the database on services each national partner was supposed to be responsible for the following tasks: collecting, validating and entering in the database information on the clinical laboratories performing diagnostic tests for rare diseases (type of test, protocol); on on-going

research programmes about rare diseases (title of the programme, name of the responsible scientist, address); on patients' organisations dedicated to rare diseases (name of the association, president, address, text of presentation); on specialised clinics dedicated to rare diseases. During the first year they were asked to establish their national methodology to do so and start collecting a few data to test the interface. They were also supposed to translate all the thesaurus and the screens in their national language.

Each partner was supposed to be provided with the computer system tools to access and update the database from their own premises. These tools had to be developed by the central team and tested to be fully operational by the end of the first contract.

For the database on services, the task to be achieved were:
- to build up and validate tools to update the central database from remote sites without endangering the database
- to train partner teams to collect, validate and format their data
- for the partners to agree on the quality scheme defined by the co-ordinating team and identify sources of information
- to nominate a scientific board in charge of the validation of the data.

I.3.2 Methodology

The database design, the query tools and the tools to update the database had to be modified as to support multi-languages. The work to be achieved necessitated 9 months of a Full-Time Equivalent.
The training of partners was done by exchanging through electronic mails, phone calls and meetings. Ségolène Aymé (project leader) spent one day in Leuven with the Belgium partners in December 2000, two days in September 2001 in Rome with the Italian partners, one day in Münich in September 2001 with the German partner. David Oziel (central database manager) spent one day in Geneva in July 2001.

I.3.3 Outcome

I.3.3.1 The new website

The new European version of the website was launched on October 15, 2001. This is a true new version, with a new graphic chart and the possibility to query in six languages. The new screens are demonstrated at the end of this report. The general information on what rare diseases and orphan drugs are has been dramatically expended.

I.3.3.2 The database of services in France

The current version of the database includes information on specialized clinics, clinical labs, research projects and patients' organizations. The content of the French database as of 1 December 2001 is:

Number of clinical laboratories	361

Number of diseases with a diagnostic test	600
Number of research programmes	1246
Number of disease with a research programme	824
Number of types of clinics	57
Number of highly specialised clinics	751
Number of support groups	211
Number of diseases linked to support groups	989
Number of support groups with a website	190
Number of website hosted by ORPHANET	70
Number of professionals cited	2199
Number of diseases linked to a website	1203
Number of distinct Url	2748
Number of orphan drugs	219
Number of disease linked to an orphan drug	207

The partners in Belgium, Germany, Italy and Switzerland started to collect the same type of data in their own country (see their activity report). The data from other countries than France are not yet entered in the database as all the informed consent are not yet collected. Data on support groups from Switzerland were entered to test the feasibility of the data entry process from remote sites, as well as data on support groups, highly specialised clinics and diagnostic tests from Italy.

I.3.3.3 The quality charter

All the partners agreed on a quality charter to be respected by all partners.

General principles

- ORPHANET is committed to maintain, update and develop an Internet database dedicated to rare diseases and orphan drugs.
- ORPHANET is committed to maintain an access that is both free and free of charge.
- Collection of data and dissemination of information abide by the legal provisions in force in the countries concerned: the professional code of ethics, any law on computing and liberties, on intellectual property rights and any law or regulation applicable.
- The information disseminated and the services developed comply with the codes and recommendations issued by the ad hoc committees recognized at the national or international level, especially concerning the respect of patients' rights, the respect of the information confidentiality, the patrimoniality of medical information, the practice of on-line medicine, and the safety of networks.
- Up to now, the codes and charters to which ORPHANET has adhered are the following: the HONcode (http://www.hon.ch/HONcode/Conduct.html), the eHealth Code of Ethics (http//ihealthcoalition/org/ethics/ehcode.html), the "Guidelines for Medical and Health Information Sites on the Internet" from the American Medical Association (http//pubs.ama-assn.org/ama_web.html) and the recommendations from the French National Board of Physicians (Conseil National de l'Ordre des Médecins).
- The database is under the responsibility of a scientific committee and an editorial board whose members are appointed for their expertise in the diseases considered on the proposal of the learned societies, the health authorities of the countries involved or any relevant organization. All the information available to the public is validated by a member of the committees before it is put on line.
- All the information is updated as often scientific news require it or at least once a year for all the data, including the administrative data.
- The methods used to collect and validate the data are described below. The mention “Central Registry (CR)” means that the procedure is operated exclusively at the Paris team level. The mention “National Registry (NR)” means that the procedure applies to every partner, including France.

Languages

- Orphanet is a multilingual project. The common language between partners is English.
- The Central Registry is in charge of maintaining the database in French and English.
- Some National registries are in charge of providing translations in their national language (Germany for German, Spain for Spanish, Italy for Italian).

Inclusion of diseases (CR)

- The list of diseases which are included in ORPHANET is defined as any condition, no matter its origin, which has a prevalence lower than 1 in 2,000 in the European population.
- The list is established by the central registry. All suggestions to create a new disease entry or delete an existing entry, or re-organize the classification must go to David Oziel (doziel@orpha.net)
- Each disease is described by a name, synonyms, key-words using the MESH terminology. Any suggestion as to modify the name, synonyms or key-words attached to a disease should also go to David Oziel.
- The NRs are responsible for the translation of these elements in their national language if different from French and English. The central registry maintains the list in English and French.
- Each disease is classified by medical speciality and placed under the responsibility of a scientific editor who is a recognised expert at the International level.
- There is at least one editor per medical speciality at the European level. The European experts form the European editorial board which is in charge of the Encyclopaedia.
- Preferably there is also one expert par speciality at the NR level. These experts form the National scientific advisory board which validates the data on services.

Textual information on each disease (CR)

- Each disease is associated with a text summarising the main characteristics of the disease, its prevalence, cause, prognosis and treatment.
- Every text is signed and dated.
- The writer is selected by the scientific editor or is the scientific editor.
- For very rare diseases the text is written directly by the CR.
- All the texts are submitted for validation to the scientific editor in charge of the disease before its release.
- The texts are updated at least once a year, and more often if new relevant scientific facts are published.
- The texts are written in an English which is understandable by any non-specialist healthcare professional.
- All the texts are written in English.
- The summaries are translated into French by the CR. Translation of the summaries into other languages has to be envisaged at the NR level providing that funding is obtained (average cost: 0.15 Eurocent per word; 200 words per summary)
- The editorial process is managed by scientific editors working at the CR.

Research projects (NRs)

- The research projects are identified using all the sources of information on research projects financed after a competitive process and a scientific evaluation.
- At the European level, the projects are those financed by the European Commission.
- NR have to establish the list of their national funding agencies. For France these sources are: INSERM, CNRS, Universities, Ministry of health and Charities like the AFM.
- The researchers are then approached to give their consent to be listed in the database and to precise the list of diseases which applies to their programme.
- The list of research projects is updated once a year.

Clinical laboratories (NRs)

- Clinical laboratories performing tests to diagnose rare diseases (no matter the methods) are identified using all the sources of information such as lists of the Ministry of Health, National reference centres, lists of professional organisations, lists established by patients support groups, lists suggested by the scientific editors.
- A questionnaire is sent to these laboratories to precise the type of activity, the methods used, the list of diseases which are diagnosed and obtain the formal consent of the responsible person.
- All the data are validated by the National scientific expert of the relevant specialty before being released. They are updated once a year.

Specialised clinics (CR and NRs)

- Types of clinics which are relevant for each disease are defined by the CR. Suggestions can be sent by the NRs.
- List of clinics of each type are established by the NRs, using all possible sources.
- A questionnaire is sent to potential clinicians to precise the type of their activity, and obtain their formal consent.
- For highly specialised clinics, the responsible physicians have to provide evidence of their expertise (list of publications, total number of patients, number of new patients per year).
- All the lists are submitted to a national expert.
- These lists are updated once a year.
- Only comprehensive lists of clinics can be released (matter of fairness).

Clinical trials (NRs)

- The on-going clinical trials for rare diseases are identified using all possible sources of information (partnership with academic and industrial sponsors, partnership with National drug agencies, web search, notification by experts, support groups and scientific societies)
- Both the sponsors and the principal investigators have to be approached to give their consent to be listed in the database and to precise the disease which applies to their trial.
- The list of clinical trials is updated at least once a year and automatically with the closing date.

Registries/ database of patients (NRs)

- Registries/ database of patients are identified using all the sources of information (notification by experts, research projects, support groups)
- At the European level, the projects are those financed by the European Commission.
- The responsible persons are then approached to give their consent to be listed in the database and to precise the list of diseases which applies to their registry.
- The list of registries is updated once a year.

Networks (NRs)

- Networks of professionals organized around a rare disease or a group of diseases are identified using all the sources of information (notification by experts, research projects, support groups).
- Only networks which are funded or administratively identifiable, are put in the database.
- At the European level, the projects are those financed by the European Commission.
- The responsible persons are then approached to give their consent to be listed in the database and to precise the list of diseases which applies to their network.
- The list of networks is updated once a year.

Support groups (NRs)

- Support groups are identified using all relevant ways including a web search and a partnership with Eurordis.
- The presidents are contacted to get their permission and establish the scope of diseases attached to their activity.

Orphan drugs (CR)

- All Orphan approved (in the US, Japan, Europe) drugs or non-orphan approved drugs with a specific indication for a rare disease are put in the database.
- The lists are established using the information available at the relevant governmental agencies.

Web sites (CR)

- Each disease is linked to relevant other web sites.
- Each web site is evaluated for its relevance, consistency, credibility.
- The URL addresses are re-checked once a month.
- The web sites are listed with a comment on the language used and a description of the type of information which may be expected.
- Only sites run under the responsibility of a public agency or a non-profit organisation are listed.
- NRs care invited to suggest National websites to Severine Rastoul (srastoul@orpha.net) corresponding to the above definition.

Design charter(CR)

- There is a design charter which has to be respected.
- The Orphanet logo is put on all documents used to run the activity.

European Website (CR)

- There is a European website at the address: www.orpha.net which is placed under the editorial responsibility of the CR.
- Other URL have been bought. They redirect to www.orpha.net. Their list is annexed.
- The static pages on the European website give general information on rare diseases, orphan drugs, the Orphanet project, the ethics charter and the procedures.
- These texts are maintained in French and English by the CR. They are translated into National languages by the NRs.

National Websites (NRs)

- NR may establish a National website of their own to give additional information which is only relevant at the country level.
- The address of the National website has to be www.orphanet.it/de/be…..
- National web sites respect the design chart and the logo
- Their front page has to give access to the CR website.

Logos

- The front page of the European website contains logos of all the agencies providing funding for the European project.
- The front page of the National websites contains logos of all agencies providing funding for the National projects.

I.4 Dissemination of results

I.4.1 Statistics of the server

The usefulness of the database was supposed to be done through the number of connections per day, number of different sites, number of countries, length of connections, types of request and analysis of messages received.
In November 2001, we have had during the month 44.425 visits from 30.428 different sites from 94 different countries. The average number of pages read was 10 per visit.
The distribution of countries is the following:

48%	France
12%	.com
3%	.edu
0.5%	.org
8%	Canada
5%	Belgium
2%	Switzerland
4%	Italy
1%	Germany
0.6%	Spain
0.5%	Netherlands
0.5%	UK

I.4.2 Analysis of messages

Despite the fact that Orphanet is not designed to answer personal requests, it is unavoidable to receive unsolicited e-mails. In order to develop an optimal methods to answer these requests and to explore all the problems raised by these e-mails, we performed a survey.
The goal of the unsolicited e-mail survey was to categorise the e-mails according to type of sender, type of information requested, whether responding according to a predetermined strategy would pose any ethical, professional or legal problems and which type of response would be most appropriate. In particular, e-mails were categorised according to the following 8 criteria: month sent, type of sender, whether patient has seen a physician, whether disease is of genetic origin, whether question is general or specific, type of question, whether response poses ethical, professional or legal problems, and most suitable type of response.
All unsolicited e-mails received by Orphanet between January 1, 2001 and June 30, 2001 were included in the audit. Data was entered directly into a Microsoft Excel spreadsheet. For each variable, total numbers and percentages were tabulated.

A total of 389 unsolicited e-mails were read and categorised according to the 8 predefined criteria. Over the 6-month period, the number of e-mails received each month was fairly constant (n=63-74), with the exception of the month of June when there was a decrease in the number of e-mails (n=39).

Results of unsolicited e-mail survey

Variable	Category	Total	%
Month e-mail sent	January	63	16
	February	69	18
	March	74	19
	April	73	19
	May	71	18
	June	39	10
Person sending e-mail	Patient	60	16
	Family or friend	129	33
	Doctor	25	6
	Other	63	16
	Not enough information	112	29
Patient already seen a doctor	Yes	94	24
	No	2	1
	Not applicable	93	24
	Not enough information	200	51
Involves a genetic disease	Yes	247	63
	No	73	19
	Not diagnosed yet	20	5
	Not enough information	49	13
Type of question	General	113	29
	Specific	276	71
Question regarding	Disease in general	74	19
	Diagnosis	20	5
	Treatment	45	12
	Prognosis	5	1
	Heredity	15	4
	Prevention	1	0
	Referral	24	6
	Support group – contact family	57	15
	Other web site	2	1
	Other	48	12
	Not related to rare disease	21	5
	Not enough information	55	14
	Unable to find what they need	22	6
Response strategy poses ethical, professional or legal problem	Yes	13	3
	No	341	88
	Maybe	35	9
Type of response according to strategy	General (no expertise)	326	84
	General (expertise)	28	7
	General and refer to MD	29	7
	Grey area	6	2

The individual sending the e-mail was most often a family member or friend of a patient (n=129, 33%), a patient (n=60, 16%), or another individual (e.g. student, support group organiser, n=63,

16%) and only rarely a physician (n=25, 6%). In 112 cases (29%), it was not specified who had sent the e-mail.

In 24% of cases (n=94), the patient in question had already seen a doctor about their medical problem. Only in 1% of cases (n=2), was it mentioned that the patient had not yet seen a doctor. In 24% of cases (n=93) the question was not applicable and in 51% of cases (n=200), it was not possible to tell whether the patient had seen a doctor.

In 63% of cases (n=247), the rare disease in question was also a genetic disease, and in 19% of cases (n=73), it was not a genetic disease. In 5% of cases (n=20), the disease had not been diagnosed yet, and in 13% of cases (n=49), it was not possible to tell.

In 29% of cases (n=113), the e-mail posed a general question, and in the other 71% of cases (n=276), there was a specific question. The majority of the questions concerned information about the disease in general (n=74, 19%), support groups or contacting a patient with the disease (n=57, 15%), or a complex, multi-part question (n=55, 14%). There were 48 e-mails (12%) asking some other question including requests for research information, epidemiological data and schemas relating to a rare disease. Twelve percent of e-mails (n=45) were about medications and treatments, 6% (n=24) requested a referral to a specialist in the field, 6% (n=22) were from individuals who could not find what they were looking for on the Orphanet database, 5% (n=21) were not related to a rare disease, another 5% (n=20) asked a specific question about diagnosis, and 4% (n=15) asked a question about heredity. Less than 5 e-mails each asked about prognosis, another web site or prevention.

It is expected that responding to these e-mails using a general strategy would pose an ethical, professional or legal problem in only 3% of cases (n=13). There is no foreseen problem for the majority of cases (n=341, 88%), and 35 cases (9%) fall into a “grey zone”. With regards to the strategy, it is expected that the majority of the e-mails could be answered using a general response (n=326, 84%), 7% (n=29) would warrant an explicit suggestion to see a physician, 7% (n=28) would require some degree of medical expertise to respond, and 2% (n=6) remain in the “grey zone” with regards to how to respond.

The materials developed as part of the strategy include: the Orphanet policy for unsolicited e-mails, online assistance documents for patients and the public and for medical professionals, and predetermined standardised e-mail responses.

The importance of having an explicit policy to manage unsolicited e-mails requesting medical information and advice is clearly needed according to current ethical, professional and legal guidelines. Deciding what form the policy should take and in particular the wording of standardised replies depends on the individual situation.
Orphanet is in a unique situation for two main reasons. First of all, Orphanet is not a medical practice, it is an information service. The Orphanet database was designed to provide online information for patients, professionals and the public. Therefore responding to unsolicited e-mails can be considered a part of this service. Unlike physicians who may respond to unsolicited e-mails with a one-line standard reply, this would not be appropriate for Orphanet where the aim is to orient and educate individuals with respect to rare diseases.

Secondly, it is ethically relevant that the information Orphanet provides is on rare diseases. This is an area of medicine where there is often very little information, making patients and their families feel isolated and discouraged. Unlike other online information services for common diseases, Orphanet has an even greater duty to respond to unsolicited e-mail requests for information, since that information may not be available anywhere else. Indeed, individuals who visit the Orphanet web site and send unsolicited e-mails are often using this resource as a "last resort", and this is clearly seen through patient comments.

Thus Orphanet has an ethical duty to respond to unsolicited e-mails for medical information and advice which is even greater than the duty of the average physician or information web site. However, the desire for Orphanet to help individuals must nonetheless be balanced by the potential to do harm if information and advice is based on incomplete information received in a single e-mail. As well, Orphanet must also bear in mind its limitations in responding to unsolicited e-mails of a medical nature in that the Information Officer who reads, categorises and responds to most of the unsolicited e-mails is not medically trained.

Developing a strategy for responding to unsolicited e-mails has allowed Orphanet to balance the desire to help with avoiding potential harm. The strategy has also allowed Orphanet to tailor the specific responses to the needs of Orphanet users. It was shown from the e-mail survey that the majority of individuals requesting information were patients and their family and friends (49%). E-mails from doctors comprised only a small proportion of the overall workload (6%). Nonetheless, it would be important to have a separate standard reply for physicians when warranted.

In over half of the e-mails surveyed (51%), it is unclear whether the patient had previously seen a physician, and in at least 63% of cases, it would also be appropriate for the patient to see a geneticist to help manage the disease and to explain the hereditary implications for the patient and their family. Thus, in the case of Orphanet's policy and advice, it would seem appropriate to provide general guidance for individuals to seek the advice of a physician, as well as a geneticist, if relevant.

Most of the time individuals asked specific medical questions (71%), which are more likely to pose ethical, professional and legal problems. There were 5% of questions asking about diagnosis and 12% asking about treatment. From the literature review on unsolicited e-mails, it would be clearly unethical to respond in any direct way to these questions. Such questions can only be addressed within the framework of a doctor-patient relationship, and should be dealt with in person. Likewise, for the 4% of individuals asking about hereditary implications, they should be referred for genetic counselling.

A large number of individuals wanted only general information about a disease and information on how to find support groups and contact other individuals who have the disease. Answering such questions would not pose particular ethical or other problems. The only issue is the workload involved. There is on average 5 such e-mails per week. It is not possible to provide personalised information to all individuals. It was thus felt that more general guidance would be the most feasible way to help individuals find the information they are looking for on the web.
A large number of e-mails (12%) came from mostly students and researchers seeking specific information on incidence rates and other detailed information which is beyond the mandate of

Orphanet to provide. Here there is no ethical imperative to respond, as there is for individuals suffering from a rare disease. Nonetheless, it is possible that these individuals could also benefit from the general advice on finding the information they are looking for on the web.

With regards to the response strategy, even with a policy in place, there will nonetheless continue to be dilemmas on interpreting the directives and a certain amount of subjective decision-making regarding the classification of the e-mails and the nature of response warranted. This was clearly the case even in the unsolicited e-mail survey. However, in the majority of cases (88%), using a general standardised response sent out by a non-medical member of staff would not appear to pose particular ethical or other problems. In only a small number of cases (7%), would professional expertise be warranted in responding to the e-mails. Whether the recipients of the standardised replies will be satisfied with such a response is a question for further evaluation.

By having produced a policy to manage unsolicited e-mails, at least it will be possible to continue to orient and educate Orphanet users while 1) greatly reducing the number of difficult ethical, professional and legal dilemmas, 2) greatly reducing the workload in responding to these e-mails, and 3) protecting patients from advice based on incomplete information by ensuring that they seek proper medical care in person from qualified professionals.

I.4.3 List of invited conferences given by Ségolène Aymé on Orphanet

As a project leader of Orphanet, Ségolène Aymé was invited 21 times within the first year of the contract to give a lecture on Orphanet. These invitations came from the Academia, the Industry and from Agencies. Here is the list:

" Orphanet : a database of rare diseases and orphan drugs "
Directorate General Public Health. Luxembourg, 8 Décembre 2000.

" Orphanet : un serveur d'information au service du développement des médicaments orphelins "
Séminaire du cabinet André Rey consultants. Hotel Marignan, Paris, 11 Décembre 2000.

" L'information par internet pour les professionnels de santé et les familles : Orphanet "
Colloque " Anomalies chromosomiques-information médicale " UNAPEI
Maison de l'UNESCO, Paris, 13 Décembre 2000.

« Le droit à l'information : l'expérience d'Orphanet »
Colloque « Les maladies rares : est-une fatalité ? ». Sénat, Paris, 16 janvier 2001

« La dimension éthique des choix collectifs : exemple des maladies rares »
XXIIème journées d'oncologie pédiatrique
Institut Gustave Roussy et Faculté de Médecine Paris-sud. Paris, 29 janvier 2001

« Les banques de données sur les maladies et les patients atteints de maladies rares »
Séminaire de formation professionnelle continue. IFIP, Paris, 6 février 2001
« Les maladies rares : constat, perspectives et possibilités d'évolution »
Audition du Conseil Economique et Social. Paris, 21 Février 2001.

« Le monde des maladies rares et l'action des citoyens »
Soirée organisée par Kiwanis International. Chateauroux. 3 Mars 2001

« Using on-line resources to help develop orphan drugs in Europe : the Orphanet initiative »
IIR Conference on Orphan Drugs, London (UK). March 28 2001

« Orphanet : the European network for rare diseases »
Symposium Il Bambino con Malattia Rara: Dopo la diagnosi quale percorso?, Conegliano, Italy, 31 Mars 2001

« Orphanet : an information system contributing to the health care in developing countries"
Colloque ENCO. Tunis, 27 avril 2001

« Sources of information on rare diseases »
EMEA, London, May 11, 2001

" Information systems on rare diseases and orphan drugs: the ORPHANET initiative as a tool to improve the provision of services in this area"
International Congress of Human Genetics, Vienna, Austria, May 28-June 2, 2001

Registries of patients : the Orphanet approach"
European meeting on Fabry disease. Nice, June 15, 2001

« How to improve the communication with patients : the Orphanet experience"
European Federation of Pharmaceutical industries association annual meeting. Luzern (Switzerland) , June 21 2001

"Improve access to new medicines and therapeutic solutions"
Emerging Biopharmaceutical Enterprises annual meeting. Luzern (Switzerland), 21 June 2001

"L'internet medical aujourd'hui"
Forum national de l'Alliance Maladies rares. Paris, 29 juin 2001

« Les maladies orphelines : état de la recherche »
IVeme séminaire de méthodologie en neurologie d'Aventis. Talloires, 30 juin 2001

« Levels of commitment to e-health ethics and quality »
E-health and quality workshop. Paris, 20 Septembre 2001

« Orphanet : a database of rare diseases and Orphan Drgs »
5a Reuniao da Sociedade Portuguesa de Genética Humana. Aveiro, Portugal. 26 octobre 2001.

« Impact of Internet on genetic diseases : the experience of Orphanet »
4° congresso nationale de la Societa Italiana di Genetic Umana. Orvieto, 30 Novembre 2001

I.5 Conclusion

The Orphanet project is developing according to the plans. The first year was a very busy one which permitted to explore all the difficulties for transmitting our five-year experience with data collection. The procedures are now well in place and should be easily adopted by the new partners. The experience also clearly showed to the partners that there was a great need in getting national funding to expand the local teams. Several countries are on the way of having complementary funding.