FINAL TECHNICAL REPORT

PROJECT : Network of Public Health Institutions on Rare Diseases (NEPHIRD)

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SUMMARY

Network of Public Health Institutions on Rare Diseases (NEPHIRD) is one of the nine projects financed by the European Commission following the decision (No 1295/99) taken by the European Parliament and Council to launch a programme of community action on rare diseases (RD), within the framework of action in the field of public health. NEPHIRD has the objective of developing models to define the epidemiological parameters of RD. Besides, the project aims at describing the situation, in terms of public health initiatives, of RD in the participating Countries as well as at developing an interactive web-site dedicated for exchange of experience and diffusion of information.

Public health institutions from 15 European Countries participated in the project which is coordinated by the Istituto Superiore di Sanità.

A web-site dedicated to the project is already developed and put in place (http://www.cnmr.iss.it/NEPHIRD/index.htm). Two questionnaires are administered – the first on various aspects of RD's problem in the participating Countries and the second as an inventory of diagnosing centres and possible sources of systematically collected epidemiological data on eight RD that were identified to represent different epidemiological realities. Following the meetings of the project management group, a general meeting (Steering committee) was held where all project participants were invited to share the results and their experiences.

The results of the questionnaire N. 1 indicated that public health initiatives have been taken recently in few European Countries, though such initiatives are not homogeneous. The inventory showed that several centres exist which handle a significant number of patients and collect epidemiological data based on local initiatives. The general meeting addressed the issues of definition and classification of RD, the possible constraints for data collection and the quality of data.

The Expert Meeting on Sociological Issues discussed such items as: who is involved in supporting people with RD, the need for a new language and more positive and accurate terminology; the need to reflect the experiences of people with RD (e.g., through expoiting the use of narratives); and finally, some key reflections to develop a culture for RD.

As concerns the role of patient's registries in the epidemiological data collection on RD, the activity of *UK Society far Mucopolysaccharide and Related Diseases Patient Registry* has been evaluated as a positive model, able to promote and support research.

Data collection on RD is relatively difficult from both the technical and the resource standpoints; efforts should be made to promote quality assurance and implement usefulness both in terms of public health and epidemiology. Overall, the consensus position was that the approach in the field of RD has to capitalise local efforts dispersed with in the European community and associated Countries.

BACKGROUND AND OBJECTIVES

Rare diseases (RD) began to surface as major public health problem since the Orphan Drug Act was approved in the United States in 1983. Several years later, the European Parliament and Council approved a similar regulation on designation of Orphan Medicinal Products (EC Regulation No. 141/2000). A decision was also made to launch a programme of community action on RD, within the framework of action in the field of public health (Decision No 1295/99). Following this decision, activities addressing the problems of RD have been streamlined and projects got approved on four major intervention areas: establishment of European Information Network, training and updating of professional skills, promotion of transnational co-operation and surveillance of rare diseases at European Community level.

Network of Public Health Institutions on Rare Diseases (NEPHIRD) is one of the nine projects approved and financed by the European Commission for the year 2000/2001. As the name implies, NEPHIRD was conceived as a forum for public institutions where sharing of opinions and experiences would take place. The project, as envisaged in its objective, was expected to tackle the approaches to estimating the prevalence, incidence and geographical distribution of RD. Therefore, the principal objective of the project was to develop model(s) for epidemiological data collection on RD at European level.

Moreover, NEPHIRD aims included a review of the ongoing activities on RD in the participant Countries as well as the development a web-site to promote an interactive information exchange.

PROJECT ORGANIZATION

Public health institutions of eleven EU-Member States and four Associated Countries as well as EUROCAT participated to the project (**List of all NEPHIRD members: see Annex - 1**). Project activities were co-ordinated by the Istituto Superiore di Sanità - ISS (National Health Institute of Italy). Representatives of the participants Countries constituted the Steering Committee to discuss and decide all strategic and scientific items. A few members of the Steering Committee were nominated to act as a Project Management Group (PMG) which was in charge of the actual organisational tasks.

PROJECT ACTIVITIES

1) **Two questionnaires**
2) **General Project Meeting**
3) **Website (**http://www.cnmr.iss.it; see NEPHIRD**)**
4) **Expert Group Meeting: Sociological Issues**
5) **Patients' and experts' Meeting: The role of patient registries to promote research**

Two questionnaires were administered (by e-mail) to all members of the project to make a rapid appraisal of the situation of RD in the participating Countries.

a) the **first questionnaire** aimed at getting information on various aspects of RD's problem in the different Countries; thus, the following issues were treated:

policy and major public health measures taken by the Government of each Country adhering to the project (articulated in terms of legislative actions, creation of an organ or a unit that deals specifically with RD, and efforts made to (re)organise health institutions to deliver services to patients affected by RD), existing surveillance or data collection systems for RD, and experience and opinion of participants on establishing a network of service delivery institutions (**Summary of the results of Questionnaire 1: see Annex 2)**

b) subsequently, a **second questionnaire** was administered as an inventory of resources on eight RD that were selected to represent different epidemiological realities. RD were grouped based on elements related to diagnosis, i.e., how easily and how early (at what age) they get diagnosed. The questionnaire was designed to identify the centres that make the diagnosis of the selected diseases and to know if they perform systematic data collection on them. (**Summary of the Results Questionnaire 2: see Annex 3).**

c) Experiences of each participating Country were presented and discussion on different issues were held in the **General Project Meeting (Minutes of the Meeting: see Annex 4).**
Moreover, Steering committee and Project Management Group Meetings were held on various occasions to decide on the model(s) to be recommended for epidemiological data collection on RD.

d) **the web site** dedicated to the project has published (April 23, 2001) with the contribution of all project members **(**http://www.cnmr.iss.it; see NEPHIRD**).**

e) **'Quality of life'** was viewed as a key interest related to developing a sociological perspective on RD. It was believed that a sociological perspective with the use of qualitative methods could enhance the project work. Therefore, an **expert meeting on sociological issues** was held in Rome on December 9-10 2002 (see **Results**).

f) The activity of ***UK Society far Mucopolysaccharide and Related Diseases Patient Registry*** has been examined as a model for the contribution of patient registries to epidemiological data collection on RD.

RESULTS

A) PUBLIC HEALTH INITIATIVES, SYSTEMATIC DATA COLLECTION AND SURVEILLANCE: INFORMATION OBTAINED BY THE TWO QUESTIONNAIRES

Public health initiatives have been taken recently in few European Countries.

Italy (National Centre for Rare Diseases) and **Denmark** (Centre for Rare Diseases and Disabilities - CHS) have organised centres that work exclusively on RD.

Moreover, the **Italian Government** has published a regulation (D.M. 18/05/2001) to establish the national network for diagnosis, treatment and surveillance of RD. The same regulation institutes the National Register of Rare Diseases (National Center of rare Diseases – ISS, Rome) for epidemiological data collection.

France has organised a date base on RD (ORPHANET).

The Netherlands has established a National Steering Committee for RD and Orphan Drugs.

Denmark is developing clinical protocols for specific diseases.

A complete overview of obtained results is given in Annexes 2 and 3.

Existing registries

National or regional registries of Cancer and Congenital Malformations are functioning well. Although such registries are not uniformly distributed throughout Europe, they are good sources of reliable information for several RD, fulfilling almost all needs, from serving as a tool for surveillance to providing epidemiological estimates.

On the other hand, there are local registries, established on the basis of local realities, which may not be shared across all the countries (e.g.: - thalassemia in Italy). There are also other registries that are shared by experts from different countries having an international characteristic (e.g. *International Registry of Alpha-1 Antitrypsin deficiency, International Fanconi Anaemia Registry*, etc). These registries, contrary to the cancer and congenital malformation registries, are disease specific. Apart from the local need and professional interest of the health workers, it is difficult to attribute any factor why registries are established on one RD but not on other ones.

Different diseases require different level of effort in different countries for their data collection. There are diseases that are diagnosed at unique centres that serve the entire

population of a Country or a region. There are also RD whose diagnosis is possibly made at various levels of the health service organisation making relatively difficult the data collection. Some centres do also have a good patient flow, handling a large proportion of patients affected by certain RD. On the other hand, besides the public health institutions, non-profit organisations do also have data on patients. Nevertheless, the reliability of such data has to be carefully assessed.

B) THE PROJECT MEETING

The project meeting organised in Rome (July 2nd, 2001) dealt with a number of questions related to RD (see the web-site http://www.cnmr.iss.it/NEPHIRD/index.htm/ for the workshop programme and Annex 4 for the minutes).

Conclusions can be summarised as follows:

a) definition of RD

Participants observed how it is difficult to define a rare condition on the basis of prevalence (5: 10.000 in the EU population) while the prevalence itself is not known;

b) classification of RD: for the purpose of developing data collection model within NEPHIRD project, the suggestion made is to work on diseases that have functioning data collection systems as one group and on those that have few or no information source as another group to initiate the data collection. Diseases that have a data collection system in place will serve as examples of ideal conditions. The data requirement in such diseases should include information for public health indicators.

According to this classification, RD are grouped in three categories and diseases are identified to represent them:

A. diseases that have an information system (data collection network)

1. congenital malformations: Gastroschisis and Limb Reduction Defects
2. cancers
3. diseases with screening programmes: Phenylketonuria
4. others

B. diseases that do not have a data collection network, and

1. diagnosis is based on laboratory/instrumental investigation: Prader-Willi syndrome, Rett syndrome, and Cri-du-Chat syndrome (5p/del)

2. clinically diagnosed: Amyotrophic Lateral Sclerosis, Myasthenia Gravis, Narcolepsy, Neurofibromatosis type-I, Aortic coarctation

C. unclassified (unknown diseases or diseases without diagnosis)

Communicable diseases are not considered in the above scheme of rare disease classification since they are already under surveillance. Similarly, several participans suggested to exclude tumours as they already are under surveillance by various Cancer Registries in different Countries.

c) Unclassified diseases/conditions are extremely rare, and it is difficult to characterise them unless similar cases are put together. Thus, a single pot where all unspecified diseases fall in gives a good opportunity to sort out such similar cases which are relevant in the context of identifying emerging diseases and early warning system. Obviously, it is a complex and difficult assignment to define the methodology of data collection on unknown disease conditions. Nevertheless, it is a possibility that needs to be entertained.

d) possible constrains

The following problems are highlighted as possible constraints:
case definition, minimum data set, delineation of the catchment area (population covered by service delivery institutes), privacy laws (restriction on data collection).

d.1) It is underlined the importance of a standard case definition that should be as much comprehensive as possible.

d.2) t is stressed, regarding the data set, not to collect information on variables that will not be analysed. Possibly, we may distinguish two data sets for the two major disease groups. Efforts should be made to collect relevant demographic, social, clinical data on diseases that represent the ideal situation.

d.3) Defining the population coverage or catchment area of a centre is another problem. For a population that is largely served (covered) by one centre we may have an estimate with a reasonably acceptable margin of error.

d.4) Concerning the restrictions on data collection, the situation is diverse in different Countries; however, there is no absolute legal barrier that inhibits to collect epidemiological data. Of course, privacy law have to be respected.

e) Quality of data

Importance was given to the quality of data. Countries do have different time of diagnosis and they have differences in diagnostic approaches and capacities. Therefore, there is a need to introduce a tool for quality assurance in every data collection activities.

C) EXPERT GROUP MEETING: SOCIOLOGICAL ISSUES

"Quality of life" was viewed as a key interest related to developing a sociological perspective on RD. It was believed that a sociological perspective with the use of qualitative methods could enhance the project work. Therefore, an expert meeting on sociological issues was held in Rome on December 9-10, 2002.

Due to the interdisciplinary approach to RD within NEPHIRD the experts involved included journalists, physicians, economists, paediatricians, bioethicists, geneticists, psychologists, sociologists, public health experts and members of Italian and European patient' associations (EURORDIS).

Who is involved in supporting people with RD

People with RDs are surrounded by other people who provide care, support and needed human contact. These include the families, the Associations for people with RD (APRD) and medical professionals. Others less closely involved include media and the pharmaceutical industry.

Families form associations because they are related to those with RDs, as a response to their needs of protection from practical, psychological and economical standpoints. Some families can receive support from telling experiences and websites can be an excellent forum for sharing stories and gaining support. Families often work very hard to gain the attention of the public to focus on a single RD; they especially need psychological support because they are dealing with illnesses on a daily basis. It is most important for a person with a RD to have a family.

APRDs often deliver knowledge of RDs to doctors who look after RD sufferers. APRDs are helpful but so also are research networks that work together with the aim of building up knowledge on RDs. There needs to be more on policy, information, treatment and cure of RDs. While knowledge building in these areas should be attained easily, the main barrier is communication between medical profession and APRD.

Families and people with RDs experience social exclusion and discrimination. APRDs help to protect families and individuals from negative experiences, by exchanging experiences and starting from 'the level of needs'. Thus, society should support APRDs.

As concerns physicians, whereas doctors deal with diseases in their daily work practices, they may not know much about RD. Families and individuals may, thus, be a source of learning for physicians. Sometimes families know more about the practicalities of RDs and they can help doctors to access services for them.

'Centralisation of knowledge on RD' is needed as much as knowledgeable doctors in local centres. In Italy, each region must have by law centres to deal with RDs. Centres should have the capacity to follow a person with a RD for her/his entire life from school, workplace, etc.; information should be provided in these areas.

Need for a new language on RD

Strong feelings were expressed about RDs by both families and 'sufferers' during the meeting. Words are changing in this area; a common language is needed in order to put forward a common point of view.

Is 'disability' an appropriate term to use for people with RDs? Or is 'those with different ability' a more appropriate one? Should we speak about 'RD sufferers' (which might be helpful to remind the probmems of human beings with RDs or it is more appropriate 'those with RD conditions'? The term 'rare disease' might even be too restricted to the medical way of thinking; thus, the term, 'rare condition' might be more appropriate.

The language needs to reflect the real experiences of those with RDs in a non-judgmental and positive (not negative) manner. These human issues of RD are important and they represent an excellent opportunity for a broader opening of the scientific standpoint. Under this respect, narratives may be used in a public context. The topic of RD may be used as a model of the problem of communication for doctors. Telling stories about RD and building narratives can also show that sometimes an illness is not devastating. Moreover, story telling could be a tool to provide good data; thus, telling a story about a RD may be used as another way both to share knowledge on RDs and to understand

chronic illness. The narrative approach may be a powerful method to think about, but it can have very serious shortcomings; thus one needs to be clear on the aim and the use of these kinds of databases.

As RDs becomes visible, they are given a right to exist. The problem of classification is a most important problem; we are building up a registrer of RDs but it is hard work and the list of RDs created by the WHO is merely a semantic invention. There is most certainly loneliness in the experience of RD, which is difficult to communicate even on this level.

In fact, the use of the terms, 'legitimation' and 'legitimacy' were important in the field of RD. In Italy, seeing a disease on a RD list means that one had a right to be treated. On the other hand, when a person with a RD is not legitimated, he/she is excluded from any discussion on RDs as well as treatment. Only with legitimation is a person with a RD treated within the national health care system.

The culture of RD: key reflections

Within the culture of RD, there is not single data set or treatment. It is very difficult to generalise about these issues, but it may be now time to start making differences between RDs especially with regards prognosis and the quality of life.

The ethical aspects of RD need to be looked at even though this area may be seen as difficult to manage. All should have access to databases but we must use the privacy criteria.

It is important that both the family and the person with RD accept the illness. If a person or families did not accept their RD, then the RD was not really under control. Research may give knowledge but acceptance is important in the culture of RD.

It is important to define terminology for comprehension; terminology is important because from the patients' points of view it is very important. The 'RD patient' does not want to be seen or to feel as different from another group of patients; it might be better to see them as 'persons needing assistance' in a continuing manner rather than as 'RD patients' or 'persons with RD conditions'.

Visibility is important in terms of priority setting and in terms of the RD disease group; usually, visibility comes from subjective information. The magnitude of the problem and the possibility of having care are two key issues; but it is necessary to find other ways to show the policy makers what the social concern for RD is besides focusing of these two issues.

Medicalisation versus de-medicalisation is another important issue. Medicalisation is a way to obtain rights of services and visibility. De-medicalisation is a way towards inclusion in the social context and provides a 'personalised approach' to patient (i.e. as a person). Inclusive language is needed in order to include both aspects of de-medicalisation and medicalisation. Also, the narrative approach is a way to include different issues at an empirical level but also to improve theoretical ideas.

The need to be legitimated is important for 'RD sufferers'. If one needs to be legitimated, he/she feels as out from the society. So this implies that the 'RD sufferer' is ignored; this is linked to the medical culture about RD. In fact, if one has a disease, which does not exist, then he/she has no possibility for a cure; it is not fair to have to ask for one's name to be included on the list to obtain rights. To be included in the list of RD is important from the economic point of view as well as from the perspective of public health support. The situation is changing because for 'common diseases' you have to pay for the costs: the 'right to citizenship' is a metaphor for the right to services. Problems exist for those experiencing poverty and being a 'RD sufferer': if one is a 'RD sufferer', he/she is probably sicker than others with usual sicknesses in society.

General Discussion on research improvement for RDs

We need to highlight the psychological support needed for the 'RD sufferer' and families. Yes, a minority can become a majority but we need centralisation of knowledge as well as centralisation of services. We need services at a local level and knowledge locally. You have to have health support and a possibility for a cure on local levels. We want the person with RD to have full information. With regards research, the 'RD sufferer' needs to give to the APRDs information but it is right that the 'RD sufferer' has to have the results of any trail. It is important to focus on getting something back (i.e. the results of the trial). It is a duty to give results back because the data belongs to the 'RD sufferers'.

We may need classification but classification based on needs. Sometimes a 'RD sufferer' does not feel involved; one way to get involved is to talk about needs. Needs and quality of life conditions are important to identify and talk about; very often for 'RD sufferers', it is more important to talk about needs and quality of life then their medical conditions. Another way for classification might be based on physical, mental or psychological problems and needs; the aim of such new classification based on needs is giving better services.

Finally, this work on sociological issues will be the basis for developing research on the quality of life of people with RD.

Executive summary on Sociological Issues

***Issues to do with the establishment of RD Data bases*:**

As more RD databases are established, a series of questions arise:

- Who will have access to these databases?
- How will the databases be used (i.e. treatment, policy purposes, etc.)?
- Will RD sufferers' privacy be maintained?
- Will the information stored in these databases be confidential?

***Issues that can be seen on a 'Meta' level*:**

- How does a RD *become visible*?
- How is a diagnosis of a RD made?
- Are RDs listed in International Classification of Disease (ICD) or is there a need to have
  them 'legitimised'?
- Are there established ways that diagnoses of RDs are made locally, regionally, nationally, internationally?
- Are 'treatment' and 'care' responses consistent within countries and between countries?
- What is the WHO's view on RDs?
- While RDs may be 'legitimate' illnesses, are there any problems with establishing 'legitimacy' in terms of resources, treatment responses and establishing service delivery?
- Do these problems vary between countries?

Levels of Responses to RD

In different Countries, there may be different level of responses (local, regional and national).

- How do these levels of responses meet the needs of RD sufferers?
- While a supra national (i.e. EU) level of response is important, how can we ensure that this level of response meets the needs of RD sufferers?

Experience of Sufferers

There may be value 'sociologically' in classifying RD according to diagnosis. This is because the experience of 'sufferers' of different RDs (whether diagnosed easily; with difficulty; as late onset or a congenital malformation) will most certainly differ and the

differences may become clearer if these diagnostic categories are used. RD sufferers can be viewed as a 'minority population' and thus, they may experience what other minority groups experience, such as social exclusion and discrimination. If RD sufferers are physically 'marked' in some way, they may experience social stigma. This may happen within their immediate families, extended families or in society. Their lives become lives 'shaped by RD'.

- What sorts of differences in relation to treatment access exist among RD sufferers whether their diseases are easily diagnosed (early onset), difficult to diagnosis, late onset or congenital?
- What sorts of differences in their experience of medical uncertainty exists among RD sufferers whether their diseases are easily diagnosed (early onset), difficult to diagnosis, late onset or congenital?
- What sorts of differences in their understanding of risk status exist among RD sufferers whether their diseases are easily diagnosed (early onset), difficult to diagnosis, late onset or congenital?
- What sorts of differences in ease of contact with medical profession exist among RD sufferers whether diseases are easily diagnosed (early onset), difficult to diagnosis, late onset or congenital?
- What are the experiences of those RD sufferers with unknown diseases?
- If their RDs are unknown, what difficulties arise for them as well as their treaters?
- What are RD sufferers' experiences in terms of disease onset, disease pathway, quality of life, expectations of mortality and life expectancy?
- How does experience of RD affect one's social status?
- Does a family need to have more economic resources than not to cope with a RD?
- If this is the case, what happens when RD occurs in families without the economic means to deal with RD?

Who are the RD Stakeholders?

- What stakes do RD sufferers have in epidemiological knowledge on RDs?
- What stakes do the families of RD sufferers have in epidemiological knowledge on RDs?
- What stakes do treaters of RD have in epidemiological knowledge on RDs?
- What stakes do policy makers have in epidemiological knowledge on RDs?

RD 'Illness Narratives'

The life stories of ill people such as RD sufferers may be illuminating and help to illustrate some of the problems they experience in their lives.
(See, Arthur Frank's work: *The Wounded Storyteller: Bodies, Illness and Ethics*, 1995).
For example, we can ask the following questions:

- What sorts of Narratives (illness stories) about their diseases and lives do RD sufferers tell?
- To whom do they tell these stories?

Arthur Frank outlines 3 types of illness narratives:

- *Restitution narrative*

Do RD sufferers outdistance mortality by rendering RD transitory?
Do RD sufferers see their body as restorable?

- *Chaos narrative*

Are RD sufferers sucked into the undertow of illness and the disasters that attend it?
Do RD sufferers see their bodies out of control?

- *Quest narrative*

Do RD sufferers meet suffering head on, accept RD and seek to use it?
Do RD sufferers use their body as 'a communicative body' that is to find new resources in themselves to accept their RDs and to communicate their suffering to others?

Other issues to consider

- Is establishing the legitimacy of a RD an important factor?
- How does uncertainty affect the life of RD sufferers?
- Is 'fear of the unknown' an important experience?
- What about the issue of 'family protection' for sufferers of RD?
- Are there 'levels of risk' within the various diagnostic categories of RD?
- What sort of approach is needed in order to be involved successfully with patient support groups (paternalist, empathic, ethical)?
- Who defines what sufferers need?
- Is there some value in looking at the field of disability, specifically at discussions on the individual and social models of disability?

D) PATIENTS' AND EXPERTS' MEETING: THE ROLE OF PATIENT REGISTRIES TO PROMOTE RESEARCH

The activity of *UK Society far Mucopolysaccharide and Related Diseases Patient*

Registry has been examined as a model for the contribution of patient registries to epidemiological data collection on RD.
The original aims of the Society far Mucopolysaccharide (MPS) and Related Diseases Patient Registry were:

- To identify by country and continent the overall incidence of MPS and related diseases
- To identify by country the regional incidence of individual MPS and related diseases
- To demonstrate to researchers and the biotechnology industry the need far ongoing research to develop future therapies.

Since its conception the Registry has been registered under the Data Protection Act in the *UK* and our sharing with data complies with current European data protection legislation.

To a greater extent the MPS Registry has now met its original aims set back in 1991. Therefore the aims of the Registry were re-evaluated and broadened to include:

- To review the epidemiology of the individual disorders throughout Europe

- To provide anonomised data to the pharma industry in respect of epidemiology and possible end points.

The data is collected through:

- European patient support groups
- Face to face, written, telephone and internet contact with families
- Diagnostic laboratories throughout Europe providing anonomised data.

To date any margin of error in terms of duplication of records has been immeasurable.

To date the Registry has contributed in a significant way to establishing the incidence of individual MPS and related diseases. It can show in many permutations the numbers of live births diagnosed with MPS by Country, region, disease, age of diagnosis, longevity.

Results of Incidence Studies from the Registry to date confirm that at least one baby

born every l0 days in the UK will be diagnosed as having an MPS or related disease (this excludes Fabry disease). This represents an overall minimum incidence of MPS and related diseases of 1:26,000.

It is also possible to reliably predict that at any one time there are approximately 74 children already born in the UK, but not as yet diagnosed as suffering fromTom an MPS or related disease.

Early results of a comparative study in Eire, Austria, Italy and Hungary support similar incidence figures.

Using data from all known surviving MPS II patients in the UK, the Registry has been able to demonstrate that 72% have Central Nervous System involvement resulting in moderate to severe learning difficulties and neuro degeneration in childhood.

Responding to requests from the Pharma Industry the Registry has been able to provide anonomised tables in relation to the genotype of individual patients and how the disease has presented clinically. It has also been possible to provide weight information to assist the Pharma Industry in working out appropriate levels of enzyme for use in Enzyme Replacement Therapy.

To conclude, through collaboration with doctors, scientists, individuals and their families as well as the network of MPS patient support organisations it is possible to compile and maintain a Registry that is verifiable and has integrity.

Minimum Data Sets

REGISTRY FOR MUCOPOL YSACCHARIDE AND RELATED DISEASES
INCIDENCE STUDIES
Unique reference number
First name initial
Last name initial
Diagnosis validated biochemically Genotype (if available)
Date of birth
Country of residence

Date of death (if appropria te) Ethnic origin

EPIDEMIOLOGICAL STUDIES FOR MPS AND ML

As above with current address, birth and death details Neurological data

ENT lvisual data

Skeletal data

Respiratory/cardiovascular data

Developmental data

Other problems

Treatment

FABRY

As above but including dermatology and renal data.

DISCUSSION

A) Importance of epidemiological data on RD

The importance of epidemiological data does not need to be underlined further. It has become a crucial element for decision making in any of the medical and public health field. All actors involved in this sector, from the family physicians to the policy makers, need to base their actions on information derived from epidemiological data.

Such information is highly needed when it comes to RD where little is known. There is lack of information even on the magnitude of most RD.

When available, it is highly discrepant and difficult to rely on (e.g. incidence rate of Amyotrophic Lateral Sclerosis in Israel was found to be 0.066 per 10,000 [Arch Neurol 1984 Feb; 41(2): 157 - 60] while it is 2.5 per 10,000 in Northern Italy, i.e. approximately 40-fold higher [Neurology 2001 Jan 23; 56(2): 239 - 44]). Nevertheless, any epidemiological data on RD is precious even if it has a quality problem; in some instances it may be the only piece of information available for evaluation.

Data collection on RD is relatively difficult both from practical and economic point of view. Consequently, efforts should be made to give it a certain level of quality and make it useful for a multitude of functions, *both in terms of epidemiology and public health*.

Apart from giving estimates of disease frequency, if possible, the epidemiological data should provide a basis to design descriptive and analytical studies as well as clinical trials. Moreover, the network of data collection should permit to establish a surveillance system on RD; a system that works not only for the already known diseases but also for the unknown and emerging ones.

On the other hand, magnitude of a disease, expressed in terms of prevalence and/or incidence alone, does not indicate the actual problems related to RD. Indicators of access to health care, adequacy of treatment, and quality of care are of paramount importance from public health and clinical points of view.

B) Approach to epidemiological data collection

Despite its well-known importance, systematic data collection is not yet a culture of some sectors of the health service. Often, valuable epidemiological and public health data/information are gathered on personal initiatives of researchers at local levels. If there are valid databases on various diseases today, it is because few motivated professionals made a huge effort to take the initiatives some years ago. The approach to be adopted in the field of RD has to capitalise on such local efforts dispersed within the European community and associated countries.

Registries of RD

It is a common understanding that Registries are the ideal sources of data that give valid and reliable epidemiological information. Nevertheless, their importance and necessity has to be evaluated on a case-by-case basis; one may wonder whether is actually a pragmatic approach and an essential step to establish a register for RD.

Running a register is really a cumbersome and costly activity that is not always effective and efficient. It is also technically difficult to ensure its quality and thus the register may even become unreliable. Case definition should be constant unless it gets changed simultaneously in all the centres where data is collected. Health operators have to be vigilant to identify cases, particularly when they are rare, and report them in time. Cases need to be searched actively from various sources in the community.

These conditions may be fulfilled through time for a specific disease with a clear case definition and relative ease to make the diagnosis or for some diseases with a relatively limited and specific population at risk. RD, as a group, however, belong neither to the first nor to the second condition. They are different in aetiopathogenesis, organ systems involved, means of diagnosis, presence of uniformly accepted standard case definition, target group affected, etc. There has to be a broad and complex system if data is going to be collected on all RD.

Alternative models

To strengthen the existing data sources and make better use of them by merging data from the various sources within Europe.

This data collection is not going to be a population based vigorous effort for complete case ascertainment as it should be for a register; in fact, it can be impossible to ensure total geographic/population coverage. Being an effort to capitalise on the existing data sources, there is not absolute need to define the population (geographic) coverage a priori. This could be done in a successive step, once the data collection is started from the institutions.

In determining their catchment area, health units have to use, by large, their experience. They could assess the situation of health units in the neighbourhood but they base their decision mainly on their own service delivery and pattern of patients' flow. Obviously, there will be cases coming from other areas. However, these will not be counted in estimating the morbidity indices. Similarly, cases from their catchment area may end up in other health units and get lost. This will underestimate the frequency of disease occurrence and it is the price to be paid for not adopting a population-based data collection system. So long as there exist specialised centres with substantial flow of patient affected by specific RD, it is more likely to get reasonably acceptable estimates of disease frequency.

There are two different options concerning data collection on RD. All agree that for a rare phenomenon a more complete and valid case ascertainment is possible if a large population is brought under surveillance. An epidemiologically significant number of cases could be identified from a large population. Nevertheless, it is also known that best quality case ascertainment for rare events is possible when we focus on a limited population and do a good follow-up and monitoring with active case finding. Therefore, it is a question of balancing the two aspects of data collection: quantity and quality.

From practical point of view, it is a question of identifying centres that give a quality case ascertainment (diagnosis) and large population coverage. Obviously, there are centres, as evidenced in the inventory and steering committee meeting, that are highly specialised in certain specific diseases with a good patient flow: it has only to be verified if they collect data systematically.

The centres that will participate in data collection should be identified by their respective country. The criteria to be applied by each country are the ones mentioned above: patient flow and quality case diagnosis. Therefore, it is imperative to select the disease/disorder before the centres.

B.1) ***Selection of diseases/disorders***

RD are numerous in number with widely different etiopathogenesis, clinical presentation and outcome. It is highly difficult to identify elements for regrouping them in various subgroups. On the other hand, it is practically impossible to collect data on each RD. It is, therefore, prudent to have a system that helps to collect data (information) on selected rare conditions so as to give a good information both for surveillance and descriptive and analytic epidemiological research activities.

Representative diseases and disorders should be selected, as far as possible. In the absence of a disease classification system adequate for RD and for the purpose of data collection, diseases could be selected based on various factors such as:

- possibility for preventive action
- presence of national or regional databases
- interest of certain groups, mainly scientists
- technical feasibility e.g. presence of clear case definition
- presence of other concomitant factors, e.g. ongoing clinical or therapeutic researches
- political visibility
- representativeness for other group of pathologies (metabolic disorders, congenital malformations, rare tumours, neurologic disorders, auto-immune diseases, etc.)

Nevertheless, none of the above cited selection criteria or their combination gives a perfect disease model that may represent other disease conditions.

This process of disease selection could also be viewed from another perspective. Having established surveillance and epidemiological research as the major purpose of data collection, it would be interesting to have information on possible risk factors. Which disease could unequivocally indicate a change in the risk factors? Or which disease condition could give a better opportunity, because of its already understood characteristics (behaviours), for studying the risk factor disease interaction? Obviously,

it is much more difficult to select disease condition according to such criteria than to the previous ones.

Moreover, it is possible to group diseases in the context of quantity and type of information. Some of the RD are conditions on which there exist data collection. The information needed on this group, obviously, would be different from the one which is collected on diseases that do not have any data collection at all.

Finally, one should keep in mind that criteria for disease grouping and selection may depend from the expert point of view. Often, experts of different discipline look at the problem from their own perspective; therefore, it has to be a consensus decision between the clinicians and public health personnel.

B.2) ***Type of information to be collected***

The type of information depends on the objectives it is collected for. Estimates of frequency of occurrence and surveillance need relatively limited information. But any effort to describe the characteristics of disease/condition and its determinants needs some more meticulously selected data set. *The information for public health indicators may be somewhat similar for most diseases; however, different information could be requested for the assessment of quality of care.*

A variable that is of interest for one disease may not necessarily be relevant for another illness. It is not also possible to list exhaustively the possible variables of interest for all RD. Diseases of similar aetiopathogenesis could have, to a certain extent, similar variables. This may help to simplify and standardise the data set to be used for such specific group of diseases. Otherwise, it is very difficult, if not impossible, to have a common minimum data set different from demographic data (age, sex, place of birth, residence, and date of disease onset and first diagnosis).

B.3) ***Organisational Set-up***

As described earlier, the initiatives on systematic data collection are not uniform both in terms of geographic distribution and disease entity. Though these initiatives could aggregate according to their specific interest, i.e. the disease, there is a need to co-ordinate in an European network all the activities of epidemiological data collection.

B.4) ***Mechanisms to ensure quality***

Generating information without ensuring the quality of data is a wastage of resources. It is now customary to ask for quality of the source before taking into consideration any data/information reported in a document. Thus, it is of paramount importance to introduce mechanisms that guarantee quality of the data collected. Both the process and the data itself could be monitored for their quality, through a managerial and a statistical approach respectively.

The elements for evaluating the quality of the whole data collection process include:

the presence or absence of clearly established objectives of data collection and case definition, capacity of the centres to make appropriate diagnosis of the disease of interest, the correlation of objectives with the data structure, the assignment of responsible person for data management, the procedures on how soon newly diagnosed cases get registered and how often the data gets analysed, the course of information flow and the mechanism for continuity in data collection, the contacts established for external feed-back, etc.

The main points that need verification from statistical point of view include:

how exhaustively cases are identified, how often the standard case definition is respected in making the diagnosis (accuracy of case diagnosis), completeness of information collected on all cases and variables, and precision of the estimate of denominator.

Clinical auditing, record linkage and capture recapture studies could be used as instruments for such purposes. Each health unit, adhering to the European network of information on rare diseases, could apply these instruments to ensure the quality of data collected.

The final aim of NEPHIRD is to set a network of networks on RD on the basis of harmonised criteria and approaches as discussed in its first year of activity.

Annex 1) Participating Countries and Organisations.

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Annex 2) Summary of the situation analysis on rare diseases: results of the first questionnaire

The NEPHIRD project envisages a feasibility study where possibilities for inter institutional collaborations are examined. It is considered , therefore, important to have an overview of the general situation of participating countries in the field of Rare Diseases (RD).

This being the objective, an open and closed type questionnaire was administered on various aspects of the problem, mainly on:

- policy measures taken by the government of each country which could be articulated in terms of legislative actions related in some way with the problem of RD, or creation of a body or unit that deals fully with and responds to the specific problems of RD or efforts made in re(organising) health service delivery addressing specifically RD.
- major public health measures taken recently addressing RD
- existing surveillance systems related to RD, i.e., on data sources and how to collect and put them together
- experience and opinion on establishing a network of health service delivery institutions so as to alleviate the first and foremost problem of patients

Participants' responses are presented in tables classified according to the major items stated above. With this background information, the Project Management Group, in its first meeting, decided to focus on few specific diseases that could represent various epidemiological realities. Accordingly, eight diseases were selected as a working list and a simple questionnaire was administered to have a clinico-epidemiological inventory. The results, here, are presented in tables.

Please note:- It is not easy and simple to get information on the situation of RD in anyone of the participating countries. Although the information is incomplete and not all project members responded, the result, anyhow, offers a simple overview of the situation in the participating European Countries.

Annex 2) Summary of the situation analysis on rare diseases: results of the first questionnaire

	CROATIA	DENMARK	FRANCE	ITALY	LITHUANIA	LUXEMBOURG	NETHERLAND
Policy measures							
• ***legal basis***	---------- No	Clinical protocol for the diagnosis, treatment and control of 11 RDs is to be approved by the National Board of Health	---------- No	Yes, An Act on Redefinition of the system of cost sharing and exemption from health service fee A Ministerial Decree on Establishing a National Register on Rare Diseases (Within the Programme of Maternal and Child Health)	---------- No	Patients affected by rare diseases are waived from medical care fee	National Steering committee for rare diseases since December 2000
• ***national public health units***	---------- No	The Centre for Rare Disease and Disabilities, established in 1990 under the Ministry of Social affairs is responsible with the responsibility for provision of counselling to persons with disabilities, their families and professionals and to collect and make available information about rare diseases and disabilities.	---------- No	National Centre of Rare Diseases (Istituto Superiore di Sanità)	---------- No		
• ***network of service delivery institutes***	---------- No	Yes, the two largest hospitals (Skejby Sygehus and Rigshospitalet) being the central referral centres for all RDs.	---------- No	The legal ground is in its last phase	---------- No	Referral to specialised hospitals in neighbouring countries	

	CROATIA	DENMARK	FRANCE	ITALY	LITHUANIA	LUXEMBOURG	NETHERLAND
Epidmiology							
data collection with registers	Regional Registers of solid paediatric tumours	---------- No	---------- No	For: Congenital Hypothyroidism Legionellosis Creutzfeldt-Jackob's disease and related syndromes Gaucher's disease	Congenital hypothyroidism & Phenylketonuria	----------	
information flow	----------	---------- No	----------	?	From neonatal mass screening with case ascertainment at Human Genetics Centre	----------	
five diseases for pilot	Fragile X syndrome Cystic fibrosis Chromosomopthies Muscular dystrophies (DMD/BMD) Skeletal dysplasias	Phenyketonuria Fragile X syndrome Osteogenesis imperfecta Thalassemia Spielmeyer-Vogt	Neurofibromatosis type-1 Marfan syndrome Achondroplasia Gaucher's Disease Fabrys's Disease	Prader-willi syndrome Narcolepsy Limb defects Phenyketonuria	Phenylketonuria Congenital hypothyroidism Cystic fibrosis Galactosemia MCAD	----------	

Current Initiatives

CROATIA	DENMARK	FRANCE	ITALY	LITHUANIA	LUXEMBOURG	NETHERLAND
The project of Ministry of Science and technology: epidmiology, clinic and biology of birth defects Since October 2000	The plan for establishing the two central referral centres	----------	Rare diseases: national registry and study models to improve the modalities of prevention, diagnosis and treatment, and knowledge in aetiopathogenesis of RDs The rare tumours: definition and validation of "the national network of rare tumours" as a model of collaboration in geographical network for the improvement of research and health service assistance in RDs Realisation of the national registry of RDs of hereditary coagulation defect	----------		

Experience on network of service delivery institutes

CROATIA	DENMARK	FRANCE	ITALY	LITHUANIA	LUXEMBOURG	NETHERLAND
Pros Possibility of early diagnosis, treatment protocols, parental counselling, and prenatal diagnosis Data base for research and surveillance Acquisition of experience in the natural course, treatment and prevention of RD ***Cons*** Difficulty to choose the referral centres	***Pros*** It is essential to establish and maintain expertise and thus harmonise clinical standards	Nobody tried to establish one	***Pros*** Early diagnosis and treatment of patients Delivery of best available service to the patients Equitable access to services Appropriate use of resources Facilitation of data collection for planing programming and research activities ***Cons*** Difficulty of identifying the referral centres Limitation of patients' choice of service provider	----------		

Conditions for establishing a register

CROATIA	DENMARK	FRANCE	ITALY	LITHUANIA	LUXEMBOURG	NETHERLAND
Obstacles Lack of awareness by the MOH on the importance of accurate diagnosis, continuous surveillance, treatment and data collection on RD	Lack of funds	----------	***Favourable conditions*** The legal and policy backing obtained at the ministerial level The establishment of a National Centre for Rare Diseases The exemption of RD patients from medical care fee The good collaboration between the NCRD and voluntary organisations and patients' groups ***Obstacles*** Lack of network and referral system for the diagnosis and treatment of RDs Poor awareness of health workers on the importance of accurate and continuous data collection Possible misunderstanding between the exiting registers and the new initiatives	***Favourable conditions*** Legal and policy backing exemption from cot sharing		

Alternative options

CROATIA	DENMARK	FRANCE	ITALY	LITHUANIA	LUXEMBOURG	NETHERLAND
Institution based data collection as a secondary option, but the ideal would be to organise data collection and validation at regional level with further agglomeration at central level	Data collection *through patient organisation*, but the problems are: incomplete membership incomplete information of the registered patients not all RDs have organisation	----------	*Institution based data collectio*n	"***only population based registe****r ensures comprehensive view about RDs*"		

Annex 3): Summary

Policy Measures taken by the EU member states on Rare Diseases

Legal basis

- Clinical protocol for the diagnosis, treatment and control of 11 RDs is to be approved by the National Board of Health (**Denmark**)
- An Act on redefinition of the system of cost sharing and exemption from health service fee (**Italy**)
- A Ministerial Decree on establishing a National Register on Rare Diseases (Within the Programme of Maternal and Child Health) (**Italy**)
- Patients affected by rare diseases are waived from medical care fee (**Luxembourg**)
- National Steering committee for rare diseases since December 2000 (**The Netherlands**)

National public health units

- The Centre for Rare Disease and Disabilities, established in 1990 under the Ministry of Social affairs is responsible for provision of counselling to persons with disabilities, their families and professionals and to collect and make available information about rare diseases and disabilities (**Denmark**)
- National Centre of Rare Diseases (Istituto Superiore di Sanità) (**Italy**)

Network of service delivery institutes

- the two largest hospitals (Skejby Sygehus and Rigshospitalet) being the centrl referral centres for all ***(Denmark)***
- The legal ground is in its last phase (***Italy)***
- Referral to specialised hospitals in neighbouring countries (**Luxembourg**)

Epidmiology *(*data collection with registers*)*

- Regional Registers of solid paediatric tumours (***Croatia)***
- National Registers for: Congenital Hypothyroidism, Legionellosis, Creutzfeldt-Jackob's disease and related syndromes, Gaucher's disease (***Italy***)
- Congenital hypothyroidism & Phenylketonuria (***Lithuania***)

Current Major Public Health InitiativesInitiatives

Croatia: The project of Ministry of Science and technology: epidmiology, clinic and biology of birth defects since October 2000

Denmark: The plan for establishing the two central referral centres

Italy:

- Rare diseases: national registry and study models to improve the modalities of prevention, diagnosis and treatment, and knowledge in aetiopathogenesis of RDs
- The rare tumours: definition and validation of "the national network of rare tumours" as a model of collaboration in geographical network for the improvement of research and health service assistance in RDs
- Realisation of the national registry of RDs of hereditary coagulation defect

Experience on network of service delivery institutes

Pros

Possibility of early diagnosis, treatment protocols, parental counselling, and prenatal diagnosis

Data base for research and surveillance

Acquisition of experience in the natural course, treatment and prevention of RD

It is essential to establish and maintain expertise and thus harmonise clinical standards

Early diagnosis and treatment of patients

Delivery of best available service to the patients

Equitable access to services

Appropriate use of resources

Facilitation of data collection for planing programming and research activities

Cons

Difficulty to choose the referral centres

Difficulty of identifying the referral centres

Limitation of patients' choice of service provider

Conditions for establishing a Register

Obstacles

a) Lack of awareness by the MOH on the importance of accurate diagnosis, continuous surveillance, treatment and data collection on RD
b) Lack of funds
c) Lack of network and referral system for the diagnosis and treatment of RDs
d) Poor awareness of health workers on the importance of accurate and continuous data collection
e) Possible misunderstanding between the exiting registers and the new initiatives

Favourable conditions

The legal and policy backing obtained at the ministerial level

The establishment of a National Centre for Rare Diseases

The exemption of RD patients from medical care fee

The good collaboration between the NCRD and voluntary organisations and patients' groups

Legal and policy backing

Exemption from cot sharing

Alternative options

- *Institution based data collection* as a secondary option, but the ideal would be to organise data collection and validation at regional level with further agglomeration at central level
- Data collection *through patient organisation*, but the problems are:

  incomplete membership

  incomplete information of the registered patients

  not all RDs have organisation
- *Institution based data collectio*n
- "***only population based registe****r ensures comprehensive view about RDs*"

Annex 4) Summary of the second Questionnaire: clinico-epidemiological inventory for 8 selected rare diseases.

1. Phenylketonuria

Country	Diagnosing Centres	Availability of data sources	Access to data sources	Other possible data sources/Remarks
Denmark	J. F. Kennedy Institute (National Centre for Treatment and Control) State Serum Institute, Copenhagen	State Serum Institute has a register	None	The Danish Centre for Rare Diseases and Disabilities (CSH) is responsible for all RD
France	National Screening Program	Yes, there is	It is accessible	
Germany	German Medizinal Unter suchungsäniter of each federal state	Yes, there is	None	
Ireland	National New-born screening centre Children's hospital, Dublin	Yes	Published in annual report	Ascertainment almost complete
Italy	National screening program at 22 centres	Yes	Aggregate data published in annual report	
Luxembourg	Laboratoire National de Santè Routine screening for newborns	Yes, there is an archive	None	
Netherlands				
Norway	National program run by Institute of Paediatrics Research, National Hospital Oslo	National screening programme has a register		
Spain	Twenty centres of early neonatal detection co-ordinated by the Commission of Metabolic Errors of Spanish Society of Clinical Biochemistry and Molecular Pathology (SEQC)	Yes, SEQC has it	Aggregate data are available from SEQC	Four regional associations of the affected people and Federation of Associations of PKU and other metabolic disorders

2. Prader-Willi syndrome

Country	Diagnosing Centres	Availability of data sources	Access to data sources	Other possible data sources
Denmark	J. F. Kennedy Institute, Glostrup Klinisk Genelisk Afdeling, København Ø	No central register		
France	Many centres (≥ 30) with molecular, cytogenetic or clinical diagnosis	None		
Germany	Institut für Humangenetik der Universität Essen	Yes	None	
Ireland	National centre for medical genetics, Our Lady's Hospital Dublin	Yes, there is under directorship of Dr. Green (ascertainment is not complete)		Cytogenetic unit, University Hospital Galway
Italy	Ospedale S. Giuseppe, Verbania Ospedale Pediatrico Bambino Gesù, Roma Istituto di genetica medica, Università di Ferrara, etc.	yes		Federazionefre le associazioni per l'aiuti ai soggetti con sindrome di Prader-Willi e loro famiglie, Torino
Luxembourg				
Netherlands				
Norway				
Spain	Of major diagnostic interest seven centres in five autonomous regions			Spanish Collaborative Study on Congenital Malformations (ECEMC) Spanish Association for The Register and Study of Congenital Malformations (SEREMAC) Four patients' associations, one at national the rest at local level

3. Rett syndrome

Country	Diagnosing Centres	Availability of data sources	Access to data sources	Other possible data sources/Remarks
Denmark	J. F. Kennedy Institute, Glostrup Klinisk Genelisk Afdeling, København Ø Centre for Sjaeldne Sygdomme, Århus N	No central register		
France	Nancy, Paris, Marseilles	Yes	None	
Germany	Institut für Humangenetik der Universität Göttingen	Yes, there is	None	
Ireland	National centre for medical genetics	yes	Yes, it is possible	
Italy	Azienda Ospedaliera Senese	Yes they have a data		
Luxembourg				
Netherlands				
Norway				
Spain	Of major diagnostic interest six centres: five in Cataluña and one in Galicia			Spanish Collaborative Study on Congenital Malformations (ECEMC) Spanish Association for The Register and Study of Congenital Malformations (SEREMAC) Three patients' associations at regional level

4. Ehlers-Danlos syndrome

Country	Diagnosing Centres	Availability of data sources	Access to data sources	Other possible data sources
Denmark	Centre for Sjaeldne Handicap, København Ø Centre for Sjaeldne Sygdomme, Århus N	No central register		
France				
Germany				
Ireland	National centre for medical genetics, Our Lady's Hospital - Dublin	Yes (but no complete ascertainment)		
Italy	Dipartimento di biochimica, A.Castellani - Pavia	Yes, there is		
Luxembourg				
Netherlands				
Norway				
Spain				ECEMC and SEREMAC

5. Amyotrophic Lateral Sclerosis

Country	Diagnosing Centres	Availability of data sources	Access to data sources	Other possible data sources
Denmark				
France	Paris, Nice	None		
Germany	Institut für Humangenetik der Universität Gießen			
Ireland	Bewmont hospital - Dublin	Have project on complete ascertainment		
Italy	Dipartimento Neuroscienze II Divsione Neurologica, Università di Torino Dipartimento Scienze Neurologiche - I° Clinica, Università di roma "La Sapienza"	Registro Piemontese Valdostano Sclerosi Laterale Amiotrofica Both departments keep their data too		AISLA Sezione Lombardia - Milano
Luxembourg				
Netherlands				
Norway				
Spain	Full Care National Centre to A.L.S Patients, Institute of Health Carlos III	Institute of Health Carlos III Hospital has a register	Aggregate data are available	One association at state and another three at local level

6. Myasthenia Gravis

Country	Diagnosing Centres	Availability of data sources	Access to data sources	Other possible data sources/Remarks
Denmark				
France	Two diagnosing centres in Paris			
Germany				
Ireland	No specific diagnosing centre			
Italy	Istituto Nazionale Neurologico Carlo Besta	Yes, it has		
Luxembourg				
Netherlands				
Norway				
Spain				Spanish Association of Muscular disorders Eight non-specific associations at local level

7. Narcolepsy

Country	Diagnosing Centres	Availability of data sources	Access to data sources	Other possible data sources/Remarks
Denmark				
France	Paris, Aix en Provence			
Germany	Institut für Humangenetik der Universität Göttingen			
Ireland	No specific diagnosing centre			
Italy	Ospedale S. Giuseppe, Fondazione Istituto Auxologico Italiano - Verbania	Just started to collect data		
Luxembourg				
Netherlands				
Norway				
Spain				Two professional associations The Foundation Sleep and Wakefulness/Ibéric Association of Sleep Pathology The Spanish Association of Narcoleptics The Register of Pharmaceutical Specialities

8. Gastroschisis

Country	Diagnosing Centres	Availability of data sources	Access to data sources	Other possible data sources/Remarks
Denmark	All County hospitals	National Register of Malformations run by The National Board of Health	Not accessible	
France		Three Registers of Congenital Anomalies Paris, Lyon Centre, East Strasbourg	Yes	
Germany		Regional Registers at Magdeburg and Mainz	None	
Ireland	Paediatric units	Registry covering Eastern Region of Ireland	Available from EUROCAT	
Italy		Five Regional Registers covering Northeast Italy Region of Tuscany Region of Emilia-Romagna Region of Latium Region of Sardinia	Aggregate data are available	
Luxembourg				The Engelhorn Foundation The CPR-Santè is re-starting a registry of congenital malformations
Netherlands				
Norway		Complete national coverage by the Medical Birth Registry of Norway		
Spain		Five local registers on congenital disorders/birth defects	Yes, it is accessible	Spanish Collaborative Study on Congenital Malformations (ECEMC) Spanish Association for The Register and Study of Congenital Malformations (SEREMAC)

Annex 5) Minutes of the first steering committee meeting of the European project NEPHIRD

July 2nd 2001, Rome

Aula Marotta

Istituto Superiore di Sanità

Introduction

The first steering committee meeting of the European project, held in Rome on 2nd July 2001, was opened with Prof. D'Agnolo's welcome address made on behalf of the President of the National Health Institute (Istituto Superiore di Sanità – ISS). He reiterated the commitment made by the Italian government, in line with the initiatives of the European Union, to address the problems of Rare Diseases (RD). Wishing a success to the meeting he underlined the public health importance of RD and the relevance of the NEPHIRD group's contribution.

The meeting was co-chaired by Dr. D. Taruscio (Project leader-National Center for Rare Diseases, Rome), Prof. G Tarsitani (University of Rome) and Prof. B Terracini (University of Turin). From the outset, the chairpersons emphasised the importance of exchange of experience and opinion sharing and how stimulant should the presentation of each participant be to explore the different possibilities for creating a network for epidemiological data collection. Subsequently, a brief description of the project, results of the questionnaires administered in the earlier phase of the project, and experience of each participating country were delivered according to the schedule.

Description of the Project

NEPHIRD is a European project that tries to tackle the problems related to prevalence, incidence and geographical distribution of RD at EU scale. It emphasises the participation of government and public health Institutions in order to maximise the impact on public health policies addressing RD. The specific objectives of the project are to develop model(s) for epidemiological data collection at EU level, to review the ongoing activities on RD in the participant Countries and to develop a NEPHIRD web-site, designed to promote an interactive information exchange.

The priority questions in the project, therefore, are related to whether and how registries or other types of data collection systems are more suitable to gather epidemiological information on RD, how population-based data can be achieved, what size of population should be covered, and what institutional frameworks should be recommended.

The project is organised in such a way that representatives of the participating countries and international organisations (EUROCAT) constitute a steering committee that will discuss and decide all strategic and

scientific items. Five members of the steering committee are nominated to act as a Project Management Group (PMG) which is in charge of the actual organisational tasks.

As an activity the project has already administered two questionnaires to make a rapid appraisal of the situation of rare diseases in the participating countries. A web site (http://www.cnmr.iss.it/NEPHIRD) dedicated to the project is already set but it needs to be improved with the contribution of other project members. Decisions need to be taken on target groups, information sources, content and presentation, interactivity, and functionality of NEPHIRD web-site

On the first meeting of the PMG a decision was made to work on models based mainly on elements of diagnosis, and thus diseases were classified as easily diagnosed or difficult to diagnose, and early or late (adult) onset. Besides, a separate group was created for congenital malformations.

A model for data collection network at EU level, recommendations and/or proposals for guidelines on data base standards and institutional frameworks, and an interactive web-site promoting the contribution of patient groups and non profit associations are the expected results of the project.

Results of the Questionnaires

The project envisages to explore the possibilities for co-operation among public health institutions in order to collect epidemiological data and exchange experiences on RD. Accordingly a questionnaire was administered to the project participants to have an overview on various aspects of the RD's problem such as,

- policy measures taken by the government of each country adhering to the project (articulated in terms of legislative actions, creation of an organ or a unit that deals specifically with RD, and efforts made to (re)organise health institutions to deliver services to patients affected by RD)
- major public health measures taken recently (following the European Parliament and Council decision – No. 1295/99) targeting RD
- existing surveillance (data collection) systems for RD, and
- experience and opinion of participants on establishing a network of service delivery institutions

The results of a clinico-epidemiological inventory on eight diseases selected by the PMG to represent various epidemiological scenarios were presented. The Project Management Group, having the results of the first questionnaire as a background, decided to adopt RD's classification based on elements related to diagnosis: 1) easily diagnosed (i.e. a diagnosis more or less certain or unambiguous), 2) difficult to diagnose (i.e. a diagnosis that does not have a standard case definition or it is difficult to identify them), 3) late onset diseases and 4) congenital malformations as a separate group.

The summary of inventory gave highlights on the diagnosing centres for those selected rare diseases, availability of systematically collected data, and on accessibility of these data. The main results were the presence of single referral centres that cover the whole nation or region, the presence of centres with a large patient flow, etc.

Experience and Suggestions of Participants

Denmark

The existing various sources of data (registries of specialists, data from the National Board of Health, National screening programmes, and patient organisations) were illustrated making reference to the future national programme on computerised patient information.

The importance of data as a tool for decision making (as in the case of designating Orphan Medicinal Products), conducting research activities, monitoring purposes or in surveillance and evaluation of the results of any intervention were described.

A suggestion was made not to limit data collection to the known diseases only; rather, there has to be an effort to establish a data set for patients who suffer from undiagnosed diseases. It may help to make comparisons of clinical features at a European level and facilitate the diagnosis of very difficult cases, as well as identify emerging diseases in time.

France

In France there is a national neonatal screening programme including Phenylketonuria, Congenital Hypothyroidism and Congenital Adrenal Hyperplasia. This programme is managed by a specific association of screening funded by the Social Security with regional associations in each region. Epidemiological data are available for Phenylketonuria at a national level.

For Gastroschisis data are available from the four French registries of congenital anomalies which cover around one fifth of the births in the country.

There are no good epidemiological data for the other selected diseases. For Prader-Willi and Rett syndromes, simple molecular diagnostic tests are possible and a few laboratories are offering them. Therefore, it is possible to collect data from these laboratories bearing in mind that an incomplete case ascertainment is probable.

Having no simple molecular or no any other diagnostic test, it is very difficult to collect data on the other rare diseases: Ehlers-Danlos syndrome, Amyotrophic Lateral Sclerosis, Myasthenia gravis and Narcolepsy. Epidemiologic data on these diseases can only be obtained on a voluntary basis from the clinicians taking care of the patients. There are also patients support groups for these diseases. However, these groups register only some of the patients.

Germany

The main scope of data collection on birth defects or RD is to determine the frequency of diseases occurrence, its trend in time and place (regional trends). Moreover, it contributes to research, to designing approaches for determining etiologic factors and adopting preventive measures, and as instrument for quality control and planning public health interventions.

Ideally, the data collection has to be complete and continuous, i.e. prospective and if possible population based. Cases should have a clear definition and get diagnosed by qualified personnel with standard examination procedures.

In Germany, there is a national screening programme for Phenyketonuria where it is possible to have reliable data. But for all the other diseases, often, hospitals or institutes are asked to report cases (disease of interest) monthly through post cards to the central registry. Subsequently, the centres receive an elaborated questionnaire to be filled for each specific disease, and the filled questionnaires are sent back to the central registry where the data are analysed.

The main problems encountered in data collection are the different German data protection rules, heterogeneity of persons/institutes involved and methods used in case diagnosis, definition bias, misclassification, heterogeneity of the diseases/birth defects, and determination of the population basis. There is no pooling of clinical data and molecular-genetic test results too.

Therefore, the main tasks would be establishing working groups for each disease of interest, selection of the participating institutes, defining the goals of the studies in a very clear way, having a standard and applicable definition of diseases, defining or standardising the investigations that are necessary for the diseases, establishing the set of information each record should have, definition of the study population, definition of a quality standards etc.

Italy

The objective of data collection is to have estimate of frequency of RD occurrence, to know their distribution in place and time, to describe the characteristics of RD and their determinants, and to conduct surveillance.

Often data are distinguished as those on prevalent or incident cases. Since data on prevalent case does not help to make surveillance, lacks follow up, and makes difficult the comparisons to be made between various results (as they may vary according to the case definition, study population and time frame), it is more preferable to work on incident cases.

In Italy, a National Register of Rare Diseases has become functional since the beginning of this year. It may be, thus, possible to have some estimates of epidemiological indices in the coming few years. The situation, however, is different in the rest of European countries and it is necessary to have parameters that represent the whole Europe than a single country.

Rare diseases are numerous in number, the list being infinite. Therefore, the need for restriction and selecting few of them to work on is obvious. On the other hand, one of the major problems in rare diseases epidemiology is how large the population be to have a significant number of cases with out loosing quality of case diagnosis.

Given the lack of systematic data collection on most RD, understanding the practical difficulty of establishing a population based data collection system for all RD and assuming that it is possible to identify centres of excellence for the diagnosis and treatment of certain RD with good patient flow, it may be possible to use them as sentinel centres for data collection, surveillance and all other related activities.

Obviously, there will be a problem in having an estimate of frequency of disease occurrence as these centres may not have a well-defined catchment area (population coverage). Nevertheless, it is not impossible, though difficult, to estimate the population coverage of these centres at any time retrospectively once we start to collect the incident cases. Efforts, therefore, should be put, to minimise the introduction of bias which is inevitable.

Malta

There are two reliable data sources in Malta: the registries of Congenital Anomalies and Cancer. Both are population based covering the whole country and they have international relations with similar registries.

The Malta Congenital Anomalies Registry (MCAR) includes all anomalies diagnosed starting from the 20th week of gestation up to the first year of life. Information regarding the infant (date and place of birth, gender, etc), the mother/father (age, occupation, illness, reproductive history, etc.), and the time and technique of diagnosis are gathered from various sources including active case collection from the public and private health units, voluntary notification by clinicians, screening programs, etc. Data from 1993 – 1999 revealed that 37.6 new-borns had congenital anomalies out of 1000 births, Phenylketonuria and Gastroschisis having

an equivalent rate of 89 per 100,000 births. Screening for Phenylketonuria is not universally applied to all new-borns.

Similar to the MCAR, the Malta National Cancer Registry (MNCR) collects information on personal data, cancer site and morphology, basis of diagnosis, therapy given, etc. from different information sources. Cases are registered according to the ICD-O classification.

Lithuania

Lithuania started to register cases of congenital malformations since 1992. The Lithuanian Registry of Congenital Anomalies (LIRECA) is instituted in the Human Genetic Centre of Santariskiu Clinics of Vilnius University Hospital and it is supposed to have a national coverage. The total population of Lithuania is estimated to be 3.6 million with 35,000 births annually. The diagnosis of congenital anomaly is made by neonatologists, paediatricians, clinical geneticists, cardiologists and pathologists using the five digit coding system of ICD-9.

According to the 1993 – 1999 data, the prevalence of congenital anomalies is estimated to be 149.8 per 10,000 births, a rate lower than the EUROCAT average estimate. Nevertheless, neural tube defects appear to be relatively more prevalent than in EUROCAT countries. Another source of information for rare diseases could be the genetic counselling system which was launched in 1971.

The Netherlands

The Dutch Alliance of Parent/Patient Organisation (VSOP) was founded in 1975 and currently has 60 member organisations. It works in information dissemination and education, stimulates research activities, monitors if the code of medical ethics are respected, etc. Being a member of the national steering committee for RD and having an international relation with other similar groups, it plays an important role in decision making at policy level.

The Dutch Genetic Information Centre, on its part, has a database which can be consulted by families on several aspects of genetic diseases including diagnostic criteria, clinical findings, prevalence, carrier detection and risk of reoccurrence in a family, treatment, prognosis, etc.

Concerning data collection at European level, it is better to establish consortia at various level for each disease group that will form a network in which patient organisations will have a fundamental role. One good example could be the network of muscular disorders. The Dutch Parent/Patient Organisation for Neuromuscular diseases (VSN), established in 1967, has founded the European Alliance of Muscular

Dystrophy Associations (EAMDA) together with other sister organisations from 20 different countries. EAMDA opened the European Neuromuscular Centre (ENMC) to stimulate and facilitate international co-operation between research groups. However, ENMC does also serve as a clearinghouse for relevant research related data. Similarly, it is possible to establish networks for other diseases that will help for epidemiological data collection at multinational level.

Spain

The Spanish health system has a network of 798 hospitals distributed through out the country: 196 belongs to the National Public Health System, 31 to CCAA, 42 to Local Administration, 15 to Ministry of Defence, 42 to other public companies, and 472 to Mutual insurance or Private Hospitals.

With in these structures there are 68 Departments of Neurology, 45 Clinical Departments of Neurophysiology, 31 Sleep disorders Units, 32 Paediatric Departments, 57 Neonatology Departments, and 11 Genetic Units (12 Lab. Molecular Genetics) that may serve as sources of data. Nevertheless, it is difficult to know which diagnosis and treatment they are involved in, and whether they keep a reliable data or not.
The situation may be different for few diseases like Phenyketonuria where there are 20 Centres of early neonatal detection, one centre for each autonomous region. These centres are co-ordinated through the Commission of Metabolic Errors of the Spanish Society of Clinical Biochemistry and Molecular Pathology (SEQC) which is responsible for quality control. For the remaining diseases selected by the project management group it is possible that a number of diagnostic centres may do the diagnosis. However, it is hard to establish which one does it appropriately with systematic data collection. Perhaps, it may be necessary, prior to any intervention, to identify the centres by the diseases they are dealing with.

There are also a good number of patients' organisations which are based on specific diseases they are affected with. Some are organised at local or regional level and some at national level. They may have data on patients; however, it is necessary to verify the quality before any type of their use.

Discussion

A number of questions were raised during the discussion on various issues starting from the definition of RD. It was observed how difficult is to define a rare condition on the basis of prevalence while the prevalence itself is not known. When a condition (disease) splits into two or more pathogenetically distinct subgroups the problem gets even worse. In the absence of a classification system adequate for RD, this remains to be a permanent problem. Nevertheless, it was stressed that the group can not change the definition of rare disease, as this is the officially accepted working definition for European Union. Therefore, any disease or disorder that affects less than 5 individuals out of 10000 population in the European Union, by

definition, has to be considered rare. There are not reliable prevalence data for all RD; however, decisions could and should be based on existing literatures when they are available.

The discussion was extended on considering tumours as rare diseases and which prevalence measure to apply. A suggestion was made to exclude tumours as they already are under surveillance by various Cancer Registries in different countries. However, it was also argued that it is illogical to do so while the effort is to develop models(s) for rare diseases to which group tumours belong perfectly well. Perhaps, tumours which are relatively frequent (e.g. breast cancer and colorectal tumours) and behave like any other common diseases need to be distinguished from those that are relatively rare. Besides, it is also important to know why and how the existing data collection systems on tumours do function.

Clarifications were given on the objectives and scope of the project and it was discussed on how to balance these with participants' expectations. Developing model(s) for epidemiological data collection at the EU level was reiterated as the principal objective of the project. Epidemiological, here, implies possibility to have estimates of frequency of RD occurrence, possibility of describing the characteristics and determinants of RD and possibility of having a RD surveillance system. Each Country, according to its own reality, could have expectations that may be different from the others. However, participants should bear in mind and work together for the common objectives of the project.

Subsequently a discussion was opened on the classification of epidemiological realities for data collection model development. It was questioned why the PMG preferred to adopt a classification based on diagnosis. In the reply, it was stated that diagnosis is a critical element in diseases' data collection. Often, evaluations are made on how complete is the case ascertainment (i.e. how many percent of the patients affected by a disease within a community are identified) and on how many of those who are labelled to have the disease do really have it: a quantitative and qualitative aspects of data collection. Therefore, certainty in case diagnosis (easily diagnosed and difficult to diagnose) and time of onset (early or late) were considered important parameters for distinguishing the main groups. It was, in fact, suggested to add a separate fifth group for early onset RD.

Participants did also point out the risk of limiting the rare diseases' horizon to genetically transmitted illnesses. It is underlined the fact that the notion of rare diseases is not in any way equivalent to genetic diseases. A purely environmental disease (e.g. lead poisoning – Saturnism) or good examples of gene-environment interaction, for instance rheumatologic or auto-immune disorders, were suggested to be considered on selection of model diseases.

Regarding congenital malformations, which are heterogeneous and account for about 35% of all RD and with well documented wide information sources, there was a strong argument that they should constitute one

group a part. However, it was noted that there is no single illness that may represent adequately all congenital malformations.

A suggestion was made to work on diseases that have functioning data collection systems as one group and on those that have few or no information source as another group to initiate data collection on them. In line with this, a relatively elaborated presentation was made on the results of inventory to give more information on the sources of data for diseases included in the initial working list.

This different way of grouping diseases for data collection, based on the presence or absence of information system, got accepted after a brief discussion. Diseases that have a data collection system in place will serve as examples of ideal conditions. The data requirement in such diseases should include information for public health indicator. For some diseases, it may be more important to have indicators of public health importance like access to service, rate of adequate treatment, attraction and migration rate as health services utilisation indicators, etc.

According to this classification of diseases we have three groups:

a) diseases that have an information system (data collection network)

f) congenital malformations
g) cancers
h) diseases with screening programmes
i) others

b)diseases that do not have a data collection network

a) diagnosis is based on laboratory/instrumental investigation
b) clinically diagnosed

c)unclassified (unknown, diseases, emerging diseases, etc).

A brief presentation was made by Prof. Tenconi on Neurofibromatosis type-I so that the group would take it as a model for one of the above mentioned groups. The disease affects around 1 out of 3000 – 3500 new-borns with variability across different population groups. It is an autosomal dominant disease with variable expressivity and a 100% penetrance at the age of 6 – 8 years. The disease is easily diagnosed having sensitive and specific diagnostic criteria. It has a risk of tumour development as a late complication. There are highly specialised units in various European countries for the diagnosis and treatment of patients and with a good potential for establishing an epidemiological network.

Communicable diseases are not considered in the above scheme of disease classification. Based on this classification, diseases were selected to serve as representatives:

A1: Gastroschisis and Limb Reduction Defects

A2: Cancer: various proposals were forwarded like Retinoblastoma, Wilms tumour, solid mass tumour, malignant nerve sheath tumours (Schwammoma), Acute Lymphocytic Leukaemia (ALL)

A3: Phenylketonuria

B1: Prader-Willi syndrome, Rett syndrome, and Cri-du-Chat syndrome (5 p del)

B2: Amyotrophic Lateral Sclerosis, Myasthenia Gravis, Narcolepsy, Neurofibromatosis type-I, Aortic coarctation, Porphyria?

A big debate was made on the disease(s) that represent (s) rare tumours. Acute lymphocytic leukaemia, which is said to have problems with delay in diagnosis and getting appropriate treatment, was refuted because it was considered to be representative of childhood or haematological malignancies. Rather a solid mass tumour or nerve sheath tumour like schwammoma, which could also be correlated with neurofibromatosis as a late complication, was suggested to represent better rare tumours. As alternatives, two other tumours (Wilms tumour and Neuroblastoma) were also proposed. Nevertheless, no consensus was reached. It was not seen necessary to identify a disease that could satisfy all the elements or that could represent perfectly all the disease conditions. Epidemiological reasons may be helpful for disease selection; however, the important thing in this disease selection, it was stated, is that the disease represents better the groups identified earlier.

Participants expressed the difficulty they have to decide on the specific diseases. The situation in their respective country is different for the different diseases and it is also different among the countries on each single disease. It was suggested also to take into consideration the administrative and other related aspects of data collection in choosing the diseases. However, it was stressed that the objective of the exercise is to identify diseases that may fit the groups created earlier, if possible not totally different from the previously selected eight diseases on which some work is already done. Participants, therefore, did not need to worry about decision making on disease conditions, perhaps, which they are not familiar with.

Explanations were given on the importance of data collection on unspecified diseases. These disease conditions are extremely rare that makes very difficult their characterisation unless similar cases are put together. Thus, a single pot where all unspecified diseases fall in gives a good opportunity to sort out such similar cases which are relevant in the context of identifying emerging diseases and early warning system. Obviously, it is a complex and difficult assignment to define the objective and methodology of data collection on unknown disease conditions. Nevertheless, it is a possibility to that needs to be entertained.

It was again raised the importance of collecting data on diseases that have already a well-established information system. Apparently it seems to be a duplication of effort; however, besides gathering some more

additional information of public health importance, data collection on such diseases is considered important as a model of the ideal situation.

Once the disease selection was finished, problems related to minimum data set, case definition, privacy laws (restriction on data collection) and delineation of the catchment area (population covered by service delivery institutes) were discussed.

As to the data set, it was stressed not to collect information on variables that will not be analysed. Information on occupation, for instance, is said to have dis-homogeneity across various study units (countries); it is a general information not often used for epidemiological analysis.

Perhaps we may distinguish two data sets for the two major disease groups. There has to be an effort to collect all relevant demographic, social, clinical data on diseases that represent the ideal situation. Finally the data sets of Malta Cancer and Congenital malformations' registries are presented as a working document to develop the list of variables (data set) for the subsequent model (s) of data collection. Nevertheless, whether to have one and unique data set or two or more based on the group or disease pathology is not yet decided.

The importance of case definition was, once more, underlined and it was commented that any case definition has to be as much comprehensive as possible. The co-ordinator of the project has taken the assignment to prepare, with the help of experts in the field, case definitions for the selected diseases and submit them to the project participants for further comments, amendments and consensus.

Concerning the constraints (restrictions on) for data collection, it was learned that there is no absolute legal barrier that inhibits to do so. The situation is diverse in different countries. Malta and Lithuania do not have a law on privacy. In France, so long as the personal names of patients are made unknown there is no problem for data collection and transmission. In Denmark, application has to be made before data are collected for any scientific purpose, etc.

The problem of defining the population coverage or catchment area of a centre was highlighted too. Centres may get patients from various regions (areas); similarly, patients may go to centres far from their residence area for the same illness that a centre in their vicinity (neighbourhood) provides a service. These situations, obviously, result an over and underestimation of disease frequency in a given population. However, we can still get good estimate by delineating the population coverage of the centre and taking in to consideration the emigration of patient to other health institute. For the population that is largely served (covered) by a centre we may have an estimate with a reasonably acceptable margin of error.

Finally emphasis was given to the quality of data. Countries do have different time of diagnosis and they have differences in diagnostic capacities too. Therefore, there is a need to introduce a tool for quality assurance in every data collection activities.

Conclusions

The meeting was closed by the project co-ordinator appreciating all the participants for their valuable contributions. Participants of the project are expected to identify the centres in their respective countries that will participate in the network for data collection. In the closing remark the project participants are kindly requested to keep in touch through the virtual office and work together to achieve the objectives set by the project.