

Minutes of the Rare Diseases Task Force
Working Group on Public Health Indicators¹

Monday 30 January 2006 10:00 – 17:00
Orphanet, Hôpital Broussais, 96 bis, rue Didot, 75014 PARIS

Attendees:

Members of the Rare Diseases Task Force Public Health Indicators Working Group:

Dr Ségolène **AYME**, Orphanet, INSERM, Paris
Dr Monika **BENE**, Hungarian Central Statistical Office, Budapest
Dr Juliette **BLOCH**, Institut de Veille Sanitaire, Saint-Maurice France
Dr Jean **DONADIEU**, Institut de Veille Sanitaire, Saint-Maurice France
Dr Paola **FACCHIN**, Epidemiology and Community Medicine Unit, University of Padova, Italy
Dr Gemma **GATTA**, Epidemiology Unit National Cancer Institute, Milan
Dr Simona **GIAMPAOLI**, Istituto Superiore di Sanità, Rome
Dr Eric **JOUGLA**, INSERM CépiDC, Le Vesinet (replacing Dr. Gérard Pavillon)
Dr Jan **KARDAUN**, Dept of Methods and Development, Statistics, Netherlands
Dr Babak **KHOSHNOOD**, EUROCAT, France (replacing Helen Dolk)
Mr Yann **LE CAM**, Eurordis, Paris (replacing Christel Nourrissier)
Dr Carmen **MARTOS**, Zaragoza, SPAIN
Dr Monica **PACE**, Servizio Sanità ed assistenza ISTAT, Rome
Dr Manuel **POSADA**, Inst de Investig en Enfermedades Rara Inst de Salud Carlos 3, Madrid
Dr Rumen **STEFANOV**, Information Centre for Rare Diseases and Orphan Drugs (ICRDOD)
Bulgarian Association for Promotion of Education and Science (BAPES) Plovdiv, BULGARIA
Dr Domenica **TARUSCIO**, Centro Nazionale Malattie Rare, Istituto Superiore di Sanità,
NEPHIRD Rome
Dr Thomas **WAGNER**, Klinikum der Johann-Wolfgang Goethe-Universität, Frankfurt

Invited Experts:

Mr Eric **FRANQUEVILLE**, Réseau Myasthénie, Plessis Robinson, FRANCE
Dr Yllka **KODRA**, NEPHIRD, Istituto Superiore di Sanità, Rome

RDTF PHI working group members unable to attend:

Dr Judith **CATARINO**, Portugal
Dr Anders **FASTH**, Göteborg University, Sweden
Dr Clare **GRIFFITHS**, Office for National Statistics, United Kingdom
Dr Mary **HEANUE**, Central Statistics Office, Cork, Ireland
Dr Lars Age **JOHANSSON**, Mortality registry, Swedish National Board of Health and
Welfare, Sweden
Dr Barbara **LEITNER**, Austria
Dr Andrie **PHINIKARIDOU**, Cyprus
Dr Torsten **SCHELHASE**, Federal Statistical Office, Bonn, Germany
Dr Mauno **VIHINEN**, Institute of Medical Technology, University of Tampere, Finland

Background and Introductory remarks:

The Working Group on Public Health Indicators is composed of members of the *Rare Disease Task Force* and invited experts. The group has been organised in order to ensure that public health indicators appropriately encompass rare diseases. Today's meeting sought to define a work plan for the coming two to three years, highlighting three main issues:

- 1) the applicability of the concept of health indicators to the field of rare diseases
- 2) The feasibility of death certificates as a source of information
- 3) The definition of rare diseases for surveillance purposes

In terms of the composition of this Working Group, it was noted that membership is flexible and can be altered to meet arising needs. Juliette Bloch (from l'Institut de Veille Sanitaire) is leader of the working group.

The meeting opened with presentations highlighting aspects of health indicator systems from various countries:

Presentation:

Juliette Bloch presented *European Community Health Indicators of DG Public Health in relation to Rare Diseases* (see [Annexe 1](#) for more details):

Public health policies aim at improving the health of citizens. Health indicators should emerge from existing data. Existing codification systems poorly recognise rare diseases.

European Community Health Indicators (ECHI) defines a detailed list of health indicators for the European Union. ECHI 2 (2001 to 2004) expanded this list of indicators. A shortlist of high priority indicators has also been developed.

The health status for rare diseases needs monitoring; among the desired goals is the establishment of related health expectancies by disease. Indicators of special interest to rare diseases include mortality age, survival rate from diagnosis, duration from first symptoms to diagnosis, related morbidity, and health expectancies. Other possible indicators include social participation or isolation, which could be defined as contact with neighbours or others, participation in activities, or associations relevant to people affected by rare disease. The number of patient associations could determine the degree of social concern.

Some possible health system indicators for rare diseases could include: neonatal screening; access to care, GP training; secondary and tertiary centres; reference centres or reference networks; highly specialized technologies, transplantation, access to innovative drugs, therapeutic trial participation, insurance coverage for costly drugs, expenditures for specific diseases, equity of access, genetic laboratories, antenatal diagnosis, public health surveillance programs, public policies for rare diseases, clinical research support and fundamental research.

Discussion:

S. Giampaoli stated the importance of identifying indicators that are universal and thus easily accessible in all European countries. She suggested death certificates as being highly feasible as all countries have them.

D. Taruscio remarked that it is also important to study the delay from onset of symptoms to diagnosis. This parameter is being measured by several registries, including the Italian National Registry of Rare Diseases, and should be a focus of the group.

P. Facchin stressed the necessity of determining the number of patients. Selecting a sample population would be more feasible than trying to obtain exhaustive data. Hospital records are interesting in that they provide a full picture of a patient and the course of a disease. While diseases must be distinguished separately, there are common traits between them and treatment can be pooled.

S. Aymé remarked that in many hospitals, coding of admissions are conducted by less-experienced practitioners. She concurred that a systematic survey was attempted five years ago and tracing patients proved difficult. She proposed following a sample of 50 of the most –frequent rare diseases, for which specific ICD codes exist.

J. Bloch pointed out that the number of patients is crucial. Prevalence across countries needs to be examined. Are there significant differences? As for coding, in France it is organised as a source of budget allocation, not for epidemiological purposes.

P. Facchin warned that codes are subject to control issues. Death certificates can have coding problems. It is not possible to determine the quality of code data. A pertinent question is whether one is dealing with a specific illness or a group of illnesses.

D. Taruscio reflected that these various concerns reveal that multiple criteria from different sources are important to obtain.

P. Facchin suggested that the area of rehabilitation can also provide data.

Presentation:

Gemma Gatta presented a report on *Health indicators in rare tumours*: (see [Annexe 2](#) for details)

Rare cancer survival: A definition and list of rare tumours was developed to carry out analysis between countries and generate a steady stream of information. 14 rare cancers were selected for study, for some of which no treatment exists. Incidence: <2-3/100,000 per year. 5-year-survival by age was analysed. As with non-rare cancers, survival decreases with increasing age. Geographical variations in Europe were considered. Diagnosis affects these variations. Survival is best in the Nordic countries, and worst in Eastern European countries.

For more detail, see the article:

Survival from rare cancer in adults: a population-based study, <http://oncology.thelancet.com> (published online December 13, 2005).

Eurochip: A DG Health project aimed at health indicators for monitoring cancer in Europe. Indicators are based on two axes: 1) the natural history of cancer and 2) prevention and screening. High priority indicators include prevention, screening, cancer registry and epidemiology, care and treatment, social and macro-economic determinants.

The definition and list of rare tumours presents standardized incidence rates (Eurocare and Seer) and offers suggestions: mortality, incidence, prevalence, survival, sentinel events, open clinical studies.

Presentation:

Manuel Posada presented *Reports from an epidemiology survey in Extremadura*, (Annexe unavailable) and a general overview of ongoing efforts on behalf of rare diseases in Spain, including rare disease framework research, health information, rare disease registries in Spain, and a health indicators strategy. He presented a description of REpLER, a network of clinical researchers, epidemiologists, pharmacologists, geneticists and molecular biology experts working to develop an epidemiological research programme on rare diseases in Spain that provides a wider knowledge of their status in clinical, epidemiological and therapeutic terms and helps to promote new social/health policies for care measures.

The health indicators listed include:

Epidemiological incidence/prevalence, et cetera

Administrative: number of expert centers, number of patients discharges, health costs, etc

Research: Public funds invested

Directory of genetic laboratories: number of genetic tests available

Acceptability: Patient satisfaction

QLRH: Preventive programmes

Number of diseases included in neonatal screening diagnostic procedures

Diagnosis delay to treatment

Number of orphan medicines available

Follow up: number of patients/diseases involved in specific follow up programmes

Prognosis

Mortality, survival

Points to be worked on in Spain: creating a rare disease network, prioritisation of health research funding. M. Posada stated that to overcome legal blocks, a general framework for a national registry has been put in place.

Presentation:

Domenica Taruscio presented a report on *Health indicators in rare diseases* (see [Annexe 3](#)):

In Italy there is a National Register of Rare Diseases, established by national regulation. In fact, in 2001 the Italian Government approved legislation that established the Italian National Network for Rare Diseases to tackle the problem of prevention, surveillance, diagnosis and treatment of rare diseases. This regulation a) listed rare diseases for which patients have diagnosis and treatment free of charge; b) since 2001, 228 regional centres have been established by Regions (official regional decisions) following the governmental regulation on rare disease; c) established at the Istituto Superiore di Sanità (ISS) the National Register of Rare Diseases, which receives epidemiological data from Regions and regional centres. An agreement between the Ministry of Health, ISS and the Regions has been established in order to co-ordinate and harmonise the regional network activities, including reviewing the list of rare conditions which will have free diagnosis and treatment.

Italy is in the process of analysing registries for rare diseases (national and regional). The ISS has organized a meeting in February 2006 to analyse efforts in this area. In addition to the National Registry, the ISS has:

a) a mortality database consisting of information from 1969 – 2002 for approximately 500, 000 deaths per year. Italian death certificates include underlying, immediate and other contributory causes of death. It is possible to analyse multiple causes of death on the Official Mortality Database. In addition, data collected and recorded from 1995 – 1999 by the Italian Census Bureau (ISTAT) is available (Information from 2000-2002 is going to be released).

b) Hospital discharge database, provided at the national level to the ISS by the Italian Ministry of Health; this database provides 10 million records per year from 2001 – 2003 and contains ICD 9 codification and other pertinent data. Later years are due to be released.

A practical example using neurofibromatosis was provided (see [Annexe 3](#) for details).

Dr. Taruscio showed participants that it is also possible to work with multiple-cause mortality. 1999 patients analysed. Using underlying cause criterion: 20 deaths from neurofibromatosis were identified. When multiple-cause mortality was applied, an additional 22 deaths were identified.

Discussion:

S Giampaoli stated that combining sources of information needs improvement. Step-wise procedures should be developed. If a patient is hospitalised several times in one year, can that fact be identified? The archives are separate. The Istituto Superiore di Sanità in Rome has permission to manage data, but there are confidentiality issues that need considering.

It was noted that each country has its own ways of compiling data.

J. Kardaun said that in the Netherlands, new legislation will ease nationwide collection of data, but diagnostic information will not be readily available.

B. Khoshnood presented some thoughts of Helen Dolk from EUROCAT, who was unable to attend (see [Annexe 4](#)): The purpose of developing indicators is for decision-making. Prevention efforts are equally important and need to be on the agenda. Selecting sentinel diseases and grouping rare diseases are two approaches that can be used in a complementary fashion.

Certain diseases are becoming rare due to higher levels of prenatal screening and pregnancy termination. S. Aymé suggested adding the variance in prenatal diagnoses from region to region. Prenatal diagnosis impact needs monitoring.

S. Aymé asked the group their opinion on the utility of the many registries existing in Europe. A list of registries available in the Orphanet database was distributed.

T. Wagner stated that existing registries are very specific. They are thus interesting in providing an overview, but using them as a starting point could evoke skewed perspectives. It is preferable to define indicators first and then see how registries could be useful. As regards death certificates, in Germany they are not considered highly reliable.

D. Taruscio commented that in Italy, they are an official source and can thus present a minimum point of departure.

S. Giampaoli stated that they are not the most reliable source, but existing validation studies can be applied.

G. Gatta concurred that many validation studies exist for cancer deaths.

P. Facchin mentioned a population-based register with a list of 10,000 patients cross-validated with other data such as mortality or rehabilitation. This data can be extrapolated to other regions and countries. An 80% or 90% validation rate is very good.

J. Donadiou agreed that determining indicators is most important. Existing indicators have limits and discrepancies, and so a step-wise approach is needed, perhaps examining diseases with the existing indicators as a first step.

Y. Le Cam pointed out that the quality of data is a clear goal, but there are contradictions in this morning's presentations and goals must be clarified to overcome discrepancies. A step-wise approach is most reasonable.

S. Aymé reminded the group of the basic goal of demonstrating the importance of rare diseases as a public health issue and suggested comparing countries as a second goal. Measures for rare diseases will issue from regions with high-quality data; i.e., registries between 1 and 7 million populations. The Venice region is an excellent example of this, but there may not be many others. Focus should be placed on existing registries and diseases that have an existing ICD code.

M. Pace wondered if using local sources could pose problems in case of an EU application for funding as one of the aims of this meeting. She pointed out that comparability issues go beyond countries and surely exist amongst regions of different countries.

S. Aymé asserted that it is impossible to have an adequate national registry. It would require too many resources and thus has never been accomplished. It is too hard to monitor a large registry. It is not an issue of regional versus national, but of population size.

S. Giampaoli pointed out that the region can validate data.

J. Donadieu noted one drawback of regional registries is that care can fall outside of the region, resulting in missing data that can lead to bias.

P. Facchin stated that health care is organised differently from country to country and bigger countries tend to organise regionally, causing flux. She urged the group to be flexible and use all reliable sources, whether regional or national.

Y. Le Cam agreed that if the first objective is to measure diseases, and regional resources are being employed, the reliability of the data must be ensured.

P. Facchin explained that in Italy, regional information is sent to a national database.

J. Bloch suggested that the group not focus exclusively on epidemiological indicators. Health system indicators that can be accessed in all countries, such as services, information on professionals, facilities, could also be used. She evoked indicators employed by the ECHI project as examples.

S. Aymé suggested that the number of registered orphan drugs could also serve as an indicator.

T. Wagner called for a survey of health system information by country, followed by an examination of registries, orphan drug registration data, and other information in order to obtain an overview of the situation.

M. Posada reminded the group that the most important goal would be to define the framework of indicators.

T. Wagner suggested it was time to propose possible indicators. Epidemiological data (birth, death, cause of death), patient information, including resources used by patients could be used. Quality of life is harder to define. If we are gathering information for political means, the data must have a shelf-life of at least five years.

J. Bloch pointed out that expenditure and other macro-indicators (number of transplants, for example) are available and should be capitalized on.

R. Stefanov asserted that epidemiological indicators do not provide enough information to adequately serve rare diseases. Health indicators must reflect the readiness and preparedness of each country in face of rare diseases.

P. Facchin pointed out that epidemiological data inform organisations and health service priorities and are thus necessary to an extent.

J. Bloch said that the two main paths of epidemiological and macro indicators are in fact complementary and not mutually exclusive.

Afternoon Session:

Presentation:

Eric Jouglà presented *Death certificate collection and coding: Current practices in Europe and appropriateness for rare diseases*: (see [Annexe 5](#) for details and samples of automated coding systems and electronic death registration)

This discourse covered mortality indicators, presenting a historical perspective and considering data comparability. Death coding was presented, including international regulations concerning classification, underlying cause definition, death certificate form, rules and guidelines, statistical definitions, and tabulation. A detailed presentation of ICD classification rules (selection, modification) was demonstrated. Data can be considered comparable if the same ICD rules and the same medical knowledge are applied.

Automated coding systems (ACS) code each condition reported on the death certificate and select the underlying cause of death. ACS include a dictionary, ICD regulations, and medical knowledge. Different automated coding systems were presented and compared. Advantages and drawbacks were analysed.

Electronic death registration was discussed, including advantages and drawbacks. International collaborations and application to rare diseases were elaborated upon (WHO, Eurostat, NCHS) and concrete examples were provided (see Annexe 5). Discussion: When asked which other European countries are working with systems similar to France, E. Jouglà responded all other countries work with a similar system and that most countries want to move toward an automated coding system. Electronic certificates are of interest, though not much progress is being made in most countries. France's heat wave of 2003 allowed the electronic system to move forward.

J. Donadieu reminded the group that T. Wagner had mentioned in the morning session that the system in Germany is quite different. Would this impact statistics?

T. Wagner stated that the physician was considered the weak point in developing a satisfactory electronic system. If the doctor does not know the correct ICD code, will (s)he make the effort to find it? The question is, what is the quality of the data being input?

E. Jouglà replied that doctors do not code and thus do not need to know the ICD coding. He then reflected that the issue depends upon the particular disease. Sudden death in an emergency situation in which the physician does not know the patient's history causes discrepancies. Yet the majority of patients die in hospital amongst professionals who have been treating the disease and know it well.

C. Martos stated that parts of Spain do not have automated coding, although the issue is being addressed.

M. Posada asserted that the system needs implementing in all European countries – although doing so is a long process. Much information is available and causes of death need validation to identify present problems.

E. Jouglu suggested starting with diseases for which ICD codes exist as a first step. Not all countries are capable of analysing multiple causes. Perhaps we could define a list of rare diseases and examine existing mortality data in terms of underlying causes via a comparative study.

J. Kardaun pointed out that using death certificates requires only lethal rare diseases being considered.

It was thus determined that hospital admission data combined with death certificate information would be more inclusive.

M. Pace reminded the group that there would be discrepancies at the coding level as not all countries use automated coding, although all use ICD classifications. She also pointed out Istat (Italian National Institute of Statistics) is in charge of the collection, coding and official release of the mortality by cause data, but at present there is no official multiple-cause data except in Australia and the US and that there is no existing international agreement for multiple-cause coding.

J. Bloch added that one must be careful grouping diseases together as prognoses vary widely within a group.

M. Posada brought up the possibility of adding rare diseases as a category on death certificates. He pointed out the danger of a systematic bias.

E. Jouglu stated that automated coding allows for the control of systematic bias.

J. Donadieu acknowledged that there are drawbacks to the various techniques, but urged the group to focus on feasibility in order to begin collaborating.

S. Aymé suggested using the approximately 50 rare, lethal diseases with a specific code in ICD 10, as a point of departure.

Presentation:

Jean Donadieu presented “*Prioritisation of rare disease for epidemiological surveillance*” (see [Annexe 6](#)). The purpose of prioritising rare diseases for public health surveillance is to produce reliable indicators. Various tools include cross-sectional studies, cohort retrospective/prospective studies, and registers. Prioritisation of rare diseases is necessary because of the number of rare diseases, and limited available resources, in order to have reliable indicators defined for a precise disease. A rational approach is warranted. Prioritisation is the only way to ensure monitoring diseases that truly need monitored. Rare disease prioritisation does not define priorities for care, basic research or suggest a moral ranking of diseases. Tools are needed determining criteria for each disease; each disease requires documentation; each disease needs ranking for public health surveillance.

The Delphi method in France has a working group including 3 patient group representatives, a panel of 110 experts, 90 of whom are medical or RD experts, 15 from insurance or institutions, 5 industrials. Round 2 contains a questionnaire mailing set to go out in February

2006 (see [Annexe 7](#)). A multiple-criteria approach with relative weight between criteria defined are expected results.

A review of a limited number of diseases – perhaps 300 - is expected by the end of 2006.

Could the criteria and prioritisation be endorsed by other countries? Is a uniform EU approach necessary?

Discussion:

J. Bloch explained that this approach is complex; the term “*criteria*” had to constantly be redefined. The questionnaire will be distributed to patient groups for response.

P. Facchin cautioned against the subjectivity of response.

R. Stefanov suggested using EMEA designated treatments as an initial criterion.

S. Aymé pointed out that there are illnesses which have no treatment but for which diagnosis is crucial.

Y. Le Cam suggested using caution with the term, “*Prioritisation*”, which may not be optimal for patient groups. Collecting information for diseases is easier for patients to comprehend. The impact of very active, vocal patient groups on disease resource policies was cited, regardless of prevalence. As regards EMEA designation, it was pointed out that the more designation exists, the more applications are put forth, as a path has already been forged.

T. Wagner suggested “*model building*” as a more neutral term than “*priority*”.

M. Posada brought up an ethical question: how to select certain diseases and not others.

S. Aymé saw the Delphi exercise as positive in bringing together stakeholders where it is often difficult to do so. Its results are interesting for decision makers.

J. Donadieu pointed out that it also increased transparency.

T. Wagner stated that it would be important to determine whether the information would have long-term relevance or whether updates via cross-sectional studies would be necessary. J. Bloch wondered whether the results might be extrapolated to other countries. P. Facchin suggested that it could be used comparatively between countries.

D. Taruscio agreed on the Delphi method and expressed her interest in collaborating on this topic.

T. Wagner brought the discussion back to the subject of determining health indicators:

Death certificates
Non-lethal illnesses
Quality of Life

He queried how quality of life indicators could be attained.

S. Aymé suggested handicap registries, pointing out that half of all handicaps stem from rare diseases. It was suggested that despite the varied impact on quality of life different handicaps illicit (blindness versus paralysis, for example) a global score for quality of life would be helpful.

B. Khoshnood queried whether “*surveillance*” was semantically correct for developing indicators. It was agreed that “*data collection*” was a more appropriate designation.

Setting Goals:

The following Work Packages were proposed:

Work Package 1:

Death certificates

Hospital discharge records (feasibility study)

Collecting data for 50 lethal rare diseases in ICD 10 (underlying cause)

Work Package 2:

Establishing a list of macro-indicators using ECHI as a source

Work Package 3:

Definition of type of diseases to be monitored

Work Package 4:

Mapping of existing data: registries, cohorts, databases, other resources

Work Package 5:

Feasibility and interest of registering patients with rare diseases in a geographically defined area

Work Package 6:

Project management and leadership

Discussion:

P. Facchin suggested involving Austria, Croatia and Slovenia.

As to the length of time to request grants, three years was deemed most desirable. It was pointed out that the discrepancies between countries necessitates a longer timeframe.

Y. Le Cam also asserted that a three year timeframe will allow for preparation of the next phase(s) of the project.

S. Aymé informed the group that there was funding available for another meeting within the year. Working independently and regrouping at the end of 2006 or in January 2007 was agreed upon.

Conclusion:

Today’s meeting permitted the group to discern appropriate health indicators and to define concrete goals in terms of 6 work packages. The following members have agreed to contribute to the following work packages (WP) or were suggested as possible candidates:

J. Karadaun will contribute to WP 1

D. Taruscio and her group will contribute to WP 1

M. Pace, upon invitation to join the project on WP1, will assess the possibility for Istat to contribute to WP 1 (see also “next actions” by G. Pavillon)

D. Taruscio proposed ISS to lead WP 2

Y. Le Cam will contribute to WP 2 (availability of orphan drugs)

G. Pavillon was suggested as a possible leader for WP 1

J. Bloch was suggested a possible leader for WP 2. Eurordis will be a partner.

Jean Donadieu was suggested as a possible leader for WP3.

Timeframe: Date for submitting WP proposals: May 2006

Date of funding if proposal accepted: Spring 2007