



Rare Diseases Task Force

**HEALTH INDICATORS
FOR RARE DISEASES:
State of the Art and Future Directions**

First Report

June 2008

Introduction

In the framework of the Health Monitoring Programme and the Community Public Health Programme 2003-2008 the EU began an integrated approach to establish European Community Health Indicators (ECHI). Several projects, described in section 3, participate in this initiative. A list of ECHI indicators is regularly updated, following the needs of healthcare provision emerging in the EU. As a member of the general EU Working party on health indicators, the RDTF is called to identify indicators that can be used for rare diseases.

There is an unmet need of RD-specific health indicators as many ‘traditional’ indicators are not applicable to the field of RD (due to the low number of patients/disease and the lack of visibility in monitoring systems). The development of relevant indicators is crucial for the monitoring of rare disease health policy and knowledge progression at the European and single member state/region levels. A collaborative European effort is always needed in the field of RD, and in particular, for health indicators (HI).

Possible actions toward the development of health indicators in this field are:

- Creation of a list of indicators relevant to the field of RD;
- Assessment of applicability of these indicators (at national/regional and EU levels);
- Selection of some specific indicators for which sources of information are already operational, to test in a pilot study;
- Publication of the information generated by the first three actions, together with:
 - a) Recommendations over data collection methodologies and tools;
 - b) Health policy recommendations based on the collected indicators;

The present report describes the political context in which indicators are being developed in the EU, the purposes of collecting indicators for RD and the legitimacy of this collection. Past and ongoing activities in the field of health indicators are also reviewed, and a list of possible RD indicators provided. Finally, information sources and data collection methodology for RD indicators are discussed.

This document was elaborated by the RDTF Working Group on Health Indicators composed by members of the RDTF and invited experts. A working document was elaborated by the scientific secretariat of the RDTF in collaboration with the University of where. This document was discussed at a workshop held in Paris on 12 March 2008. Contributions from the participants were incorporated to the working document to constitute the present report.

1. The political context: Rare Diseases in the EU

Rare diseases (RD) are life-threatening or chronically debilitating diseases with a low prevalence and a high level of complexity. Most of them are of genetic origin; others include rare cancers, auto-immune diseases, congenital malformations, toxic and infectious diseases. A Community action programme for RD was adopted by the EU for the period 1999 -2003. This programme defined a disease as rare when it affects less than 5 persons per 10 000. On the basis

of the present scientific knowledge, between 5 000 and 8 000 RD affect 3-6% of the total EU population at one point in life. This translates into approximately an average of 246 000 patients per disease in the EU with 27 Member States (MS).

RD is heterogeneous in terms of prevalence, age of onset, clinical severity, and outcome. These, all together account for a big part of the early-life deaths and life-long disabilities in the European population. RD share issues of invisibility with respect to most health care policies, and the healthcare provision for these diseases differs significantly in EU member states/regions with respect to its availability and quality. RD call for special and combined efforts to prevent significant morbidity and premature mortality, improve quality of life and socio-economic potential of affected persons, and solve regional inequalities in provision of care.

In January 2008, the Second Program of ‘Community Action in the Field of Health’ 2008-2013 of the European Commission has come into force. The Programme aims to: 1) Improve citizens' health security; 2) Promote health, including the reduction of health inequalities; 3) Generate and disseminate health information and knowledge.

The third strand includes:

- Action on health indicators and ways of disseminating information to citizens;
- Focus on Community-added-value action to exchange knowledge in areas such as gender issues, children's health or rare diseases (RD).

Information in healthcare is a main objective of the EU policy for the coming years, and indicators are the necessary information tools to guide and evaluate health policies interventions, particularly in those fields where these policies are missing or are inadequate, and where important European values such as equity and fight against discrimination are to be fulfilled, such as in the field of rare diseases.

More information on the Health Strategy and Program are available at: http://ec.europa.eu/health/ph_overview/strategy/health_strategy_en.htm

In the framework of the New Health Strategy, the Commission decided to develop a specific action on RD, which resulted in a Public Consultation: ‘Rare Diseases: Europe’s challenge’. The text of the public consultation was drafted by an expert panel composed of RDTF members and members of the Commission; the EC is planning to publish a ‘Commission Communication on a European Action in the Field of Rare Diseases’ in the second half of 2008. The Communication constitutes an important legal basis for RD initiatives at EU level, setting the main priorities in this field. The most important objectives in the European Action on RD are:

- Strengthening cooperation between EU programs;
- Encouraging EU Member States in developing national RD health policies
- Ensuring that common quality standards are developed and shared everywhere in Europe

The need of **health indicators for rare diseases** is crucial for the assessment of the present situation of RD and the monitoring of health policies in this field. Furthermore, the Communication pays significant attention to the visibility of RD also through the use of indicators, encouraging the compilation of existing sources as well *‘as the definition of a realistic and meaningful set of indicators in the areas of orphan drug availability and accessibility, centres of expertise, and RD policy initiatives at the MS level’*.

2. Definition and Objectives of Health Indicators for Rare Diseases

Indicators are parameters, or a set of parameters, to evaluate the health status of a population and the impact of health policies on this status. Indicators should be informative over the health status and sensitive to changes over time. The development of valid and relevant information is a prerequisite for planning efficient health interventions, health services, and allocation of resources.

In the field of RD, information tools have to be tailored to the specific needs and problems of this field. Due to the heterogeneity of RD, the low number of patients/disease and the geographical spread, many indicators used for more common diseases are not applicable. In the RD field, coordination and pooling of resources are the necessary basis to generate indicators.

As a general rule, indicators should be:

- **Relevant** to the question that is being posed
- **Reliable:** giving the same value if the measurement is to be repeated in the same manner on the same population
- **Useful:** providing information that is useful to decision-makers and can be acted at several levels (local/national/international)
- **Valid:** effectively measuring what they are meant to measure
- **Applicable** to the existing reality (to data collection tools and health policies)
- **Feasible** on an as-large-as possible geographical scale

Main purposes of health indicators for RD are to:

- a) Measure RD globally and individually as a public health issue**
 - For visibility/advocacy
 - To identify targets of interventions
 - To allocate appropriate resources
- b) Enable surveillance of status and trends to**
 - Measure the impact of prevention, diagnosis/screening and care
 - Identify etiological and modifying factors
 - Analyze geographical differences and changes over time
 - Document influence of health policy measures
 - Guide of new research initiatives
- c) Provide efficient and consistent reporting mechanisms**

The first purpose, '*Measuring RD as a public health issue*', is almost unique to the situation of RD and it speaks of the situation of invisibility that characterizes them. When diseases are invisible in classification systems, hospital charts, death certificates, or are misdiagnosed, these diseases are invisible also for the healthcare systems. In the RD field, collection of data finalized to epidemiological indicators, e.g. incidence, prevalence, and contribution to premature mortality and to morbidity, also respond to the aim of unrevealing the burden of disease and advocating the need for intervention.

The second and third purposes deal with the comparability of data and sensitivity of the indicators. In the event that data on RD are available, there is often discrepancy between countries/regions in the kind of data and the manner in which they are collected (e.g. data of incidence, prevalence and mortality for public health purposes are not always consistent with data collected for clinical and etiological studies). Comparability of data is an issue even more important for RD than as for common diseases, therefore the risk of losing signals of efficacy of healthcare interventions is higher in RD than as in more common diseases. A collaborative European approach toward common data collection methodologies is required.

The field of RD needs indicators that are particularly sensitive. An indicator is as sensitive as its ability of revealing changes in the issue/factor of interest. For example, indicators such as mortality rates can have low sensitivity to change in very rare diseases, due to the small numbers involved. However, the same indicators can become more sensitive in the presence of e.g. a very effective treatment or prevention action.

In the past years, the RDTF and related projects have undertaken several initiatives to improve data collection. In particular, efforts have been aimed **to the creation of a better classification system** for RD, which can unmask the presence of RD in hospital discharge charts and death certificates. To this aim, the RDTF working group ‘Coding and Classification of RD’ is currently acting as Advisory Group to the WHO in the ICD (International Classification of Diseases) revision process, from ICD10 to ICD 11. Specific initiatives toward a better classification in the field of rare tumours have been carried on by the projects EuroCare and RARECARE, among others.

Part of the work of the RDTF has been directed towards contributing to the creation and establishment of quality standards of **databases and registries**, so as to facilitate comparability of data for epidemiological and public health purposes.

3. Legal basis of Health Indicators for RD

One of the major aims of the EC is to produce comparable information on the health status of populations and health systems. This information must be based on common indicators agreed upon across Europe. **Legal basis for health indicators** is provided by several actions of the past Program of Community Action in the Field of Public Health 2003-2008 and in the New Health Strategy 2008-2013.

In particular, looking at the New Strategy, the ‘Health information and Generation of Knowledge’ strand states that attention is to be paid to ‘*develop a sustainable health monitoring system with mechanisms for collection of comparable data and information, with appropriate indicators; ensure appropriate coordination and follow-up to Community initiatives regarding registries.....; collect data on health status and policies; develop, with the Community Statistical program, the statistical element of this system*’. These points are identified as strategic directions and as areas to be supported with specific initiatives by the FP7 Program.

Other current and future actions legitimating the development of indicators include:

- A Regulation from the Council and the Parliament, to create (Eurostat) a statistical framework for data collection on health and safety at work in some areas;
- A contract agreement between the EC and OECD for the development of indicators in several areas, including indicators on Health Care Quality (report dated 30 Oct 2007);
- The development and maintenance of a System of Community Health Indicators (the ECHI project and projects under the umbrella of the Working Party on Health Indicators)
- The elaboration, in 2009, of a proposal for a ‘Commission Communication on the European Health Information, Knowledge and e-Health System’ with indication of the national and EU responsibility on data collection, the interoperability of different health indicators systems, and a code of good practices on health information.

Legal basis for the development of health indicators in the field of RD is provided by the New Strategy through the already mentioned third strand: ‘*Action on health indicators and ways of disseminating information to citizens; Focus on Community added-value action to exchange knowledge in areas such as gender issues, children's health or rare diseases*’. The implementation of the Strategy realized through the EU Public Health Work Plan 2008 acknowledges these bases; initiatives to be supported include ‘*Building capacity for development and implementation of effective public health policies particularly in areas of high need*’, such as the area of RD. The necessary basis for health policy development and implementation is the availability of effective health indicators.

As described in section 1 of this paper, in 2007, the EC initiated the a public consultation that will lead to a final ‘Commission Communication on a European Action in the Field of Rare Diseases’, to express the needs of the RD community. A Community action in the RD field is legitimated by the principle of subsidiarity (*in which the Union does not take action –except in the areas which fall within its exclusive competence- unless it is more effective than action taken at national, regional or local level*) and the legal basis for EU action in the Area of Public Health (art. 152).

As previously mentioned, the need for meaningful and realistic health indicators in RD is indicated in a specific paragraph of the Communication. Once finalized, the RD Communication shall be one of the most important legal bases for all European initiatives in the field of RD.

4. European Health Indicators Projects

Under the current and the incoming public health program, the work to develop European Common Indicators (ECHI) is being conducted through Working Parties and Task Forces that create a prototype for the future health monitoring system, coordinated under the ECHIM umbrella. Each working party/task force contributes in developing indicators in their own areas of expertise. Activities toward the development of indicators cover five phases: analysis of data needs in their respective area; definition of indicators and quality assurance; technical support for national efforts; data collection at EU level; reporting and analysis; and promotion of the results.

Main projects involved in the development of Health Indicators in the EU are listed on Annex 1:

5. Health Indicators for Rare Diseases

Categories of health indicators for RD, based on specific purposes, should include:

- a) Contribution of RD to morbidity and mortality
- b) Socio-economic impact
- c) Availability of appropriate Health Services
- d) Information, research, technology development
- e) Monitoring of geographical differences in Europe
- f) Surveillance of status/trends over time

A list of RD health indicator classes and of potential relevant indicators in each class was discussed during the Paris workshop, in terms of their relevance and availability, and appropriateness of data sources. The following emerged as the most valid candidates for starting studies on feasibility and comparability of data:

- a) Contribution of RD to morbidity/mortality**
 - Prevalence, per disease and global
 - Incidence, per disease and global
 - Death rates (Mortality)
 - Hospital admissions
 - Contribution to mental/physical/neuro-sensory disabilities
 - Contribution to transplantation
- b) Socio-economic impact**
 - Impact on families (economic, social, psychological)
 - Annual budget to cover orphan drugs
 - Contribution of consanguinity
- c) (Availability of appropriate) Health Services**
 - Genetic testing: Laboratories certified/accredited
 - Availability of genetic counselling
 - Number of diseases for which there is biological testing
 - Prenatal diagnosis (impact on RD prevalence)
 - Neonatal screenings
 - Age at diagnosis (diagnosis delay)
 - New orphan products approved by EMEA
 - Availability/accessibility of orphan drugs with EMEA approval
 - Number of Patients' Organizations and number of diseases covered
- d) Information, research, technology development**
 - Number of RD with an ICD code
 - RD for which good practice guidelines are available
 - Registries and databases for RD, geographical coverage
 - Number of ongoing clinical trials for RD

e) **Equity, EU initiatives**

- Countries with specific funding processes and Plans for RD
- European reference networks for RD
- European registries
- EU Funding programs for RD (research, public health)
- Courses, congresses and seminars on RD

Some of the proposed indicators are particularly important for **surveillance of status and trends**:

- Prevalence, incidence, mortality
- Laboratories accredited for genetic testing
- RD for which a diagnostic testing exists (e.g. genetic, biochemical)
- Neonatal screening in place
- Impact of prenatal diagnosis
- Diagnosis delay
- New Orphan products approved by EMEA
- % of marketed drugs among those with EMEA approval
- Perceived health (quality of life – QoL)

6. Methodology for RD indicators

Due to the invisibility of RD in classification and health information systems, data collection is a critical limiting factor in the development of health indicators for RD. Therefore it is important to check the comparability and “fitness for use” of the data that are already being collected in this field. Furthermore, efforts have to be made in identifying new relevant indicators for which data are not being collected yet but whose collection appears to be feasible at the European level. As RD is very heterogeneous, it is impossible to think of generating specific indicators for each of them. It can be useful to select a limited number of diseases/groups of diseases to be used in pilot feasibility studies regarding RD health indicators.

a) Selection of “pilot” RD to monitor with specific indicators

Possible selection criteria:

- RD that are relatively “frequent” (and with an ICD-specific code);
- Groups of RD with similar characteristics (e.g. similar age of onset/survival/level of disability);
- Availability of screening measures of known risk factors and/or of effective treatments;
- Relevance of the disease (e.g. highly invalidating, fatal, rapidly progressing, high impact on families and the society);
- Data already being collected on a systematic basis;

Possible selection method:

The RDTF Working Group on Health Indicators (WGHI) agrees on the selection criteria and proposes a list of pilot diseases; from among these, the diseases to monitor will be chosen on the basis of a written enquiry (members of the WGHI and to other relevant experts/stakeholders in the field) using a consensus method (see Annex 1). In alternative, a consensus meeting with relevant experts will be organized.

b) Selection of indicators to be monitored in the pilot RD

For each pilot disease, the already existing sources of data will be revised.

Possible general selection criteria:

- Indicator is relevant; data are already being collected in a large geographic area of the EU in a common somewhat standardized manner;
- Indicator is relevant; data are being collected in a large geographic area of the EU in different ways but the data can be considered comparable;
- Indicator is relevant; data are not being collected or only partially collected at present but could be easily implemented in large areas of the EU.

Possible selection method:

As for the selection of pilot RD, possible indicators will be proposed by the WPHI and a list will be circulated among experts in the field/relevant stakeholders, with final consensus on the list. In alternative, a consensus meeting with relevant experts will be organized. Once selected, feasibility study of the indicators will be carried on with different sources and methodology according to the type of indicator and the type of disease.

Other issues relevant for the selection of RD HI:

Data comparability issues are present in any action aimed at the development of indicators. Some issues were presented in the last OECD report, having to do with use of data that are non-nationally representative, administrative vs. survey data, and harmonization of data-recall periods for cancer survival. In defining health indicators for RD, a tailored consensus should be found on the requirements of data in terms of comparability at the beginning of the selection. For this reason, an inventory of the available sources for each indicator will be performed prior to the choice of the indicators to monitor in the pilot RD. Besides comparability of data, relevance, reliability, sensitivity, usefulness, and validity of the indicators will be taken into account in the selection procedure.

Relevance of the indicators will be based on the following: a) it must be a tool for health policy; b) it must be related to a priority health problem; c) it must allow comparisons across regions/countries over time; d) data should be/become readily available; e) the choice of a set of indicators must be integrated into a more global perspective of the health information system.

As a result of the selection it should be possible to create e.g. a **Minimum set of indicators** that can be collected on a large geographical basis plus another small group of indicators with narrower geographical coverage but high relevance and reliable sources of data.

7. Data sources for Rare Diseases Indicators

Currently available sources of indicators include:

- **Death certificates**
- **Hospital charts**
- **Registries:** National/regional, international
- **Scientific/Clinical databases**
- **Dedicated web portals**
- **Patients' Organizations**
- **Ad hoc clinical studies / Ad hoc surveys**
- **Surveillance systems**
- **Literature**

Death certificates: A source that contains mortality data and might be used for assessment over time and between countries. Demographic data such as age, gender, place of residence, marital status and occupation are also recorded. Data which are national are available and they are usually verified by national statistic institutes. Comparability of death certificate data is difficult, depending on the accuracy of the local registration system, the coding of the disease, and the type of professional who codes. Several initiatives toward uniform death certificate records across Europe are ongoing (Eurostat). Electronic death registration is also taken into account and being implemented in some countries (e.g. in France). To use them as source of prevalence data for RD, attention has to be paid to avoid overlap with hospital admission charts.

Hospital charts: hospital admission or discharge data are increasingly available in Europe, and several EU countries are keeping national databases of hospital admissions. However, most hospitals are still using ICD 9 and several RD are not coded, thus they can be misclassified on hospital charts. The WGHI thinks that for a certain number of well-known (well-coded) RD, hospital charts represent a valid tool to monitor indicators (e.g. prevalence, morbidity); for these diseases, a collection of hospital chart data could be asked to Eurostat. Hospital access/discharge data to be used for indicators such as prevalence should be based on person, not on episode, to avoid data duplication.

Registries: Registry of all RD are not available in any country. Italy has a systematic registration system of a large subset of RD in a few regions. International registries/networks of registries are important sources of information for specific diseases, for which they can provide additional data (e.g. diagnosis delay and quality of life). Registries of patients treated with orphan drugs allow gathering evidence on effectiveness of treatments. Handicap and rehabilitation registries, if available, may provide useful complementary information.

Scientific/clinical database networks: can contain genetic, epidemiological, clinical, and biochemical data. Provided that data are of adequate quality, they can generate information over prevalence/incidence and mortality, and several additional data (e.g. quality of life, diagnosis delay) on the specific disease. In most cases, databases are non-population-based, and further work on converting databases data into population-based data may be necessary to achieve adequate representation of the population affected.

Dedicated web portals: Orphanet is a source of epidemiological data and information over health services and orphan drugs. The Orphanet database for RD provides information for approximately 6,000 diseases. It provides a comprehensive encyclopaedia of RD; a directory of

professional services in 36 countries; a directory of expert clinics, medical laboratories, research projects, registries and patients' organizations in the field of RD; a database of orphan drugs with their stage of development and availability in EU countries; and a range of other services for specific categories of stakeholders.

Patients' Associations and Organizations: are sources of information. Eurordis, the largest European patients' umbrella association, publishes regular reports with information on orphan drug availability, pricing and marketing. Projects collecting health status and socio-economic status data (e.g. education and employment) for some RD are ongoing, using survey methods.

Ad hoc clinical studies: clinical studies can be used to investigate parameters such as prevalence, incidence and mortality in selected populations with a specific RD. Cohort studies (prospective/retrospective) might be appropriate study designs to monitor indicators in RD populations (e.g. cohorts of newborns with a certain genetic defect, or patients in a European database) since the low numbers of affected patients can render the conclusions of these studies generalizable to all patients with that specific RD.

Cross-sectional studies on sufficiently representative populations might be useful to investigate how different indicators are associated with a certain disease/group of diseases.

Ad hoc surveys: survey data (household surveys, sample surveys, ad hoc surveys) are commonly used tools for monitoring health indicators. Available literature reports suggest possible discrepancies between data generated by administrative records and surveys; however the last OECD report (30 oct 2007) on healthcare quality indicators shows that, with an improvement of data collection, there is no systematic difference anymore between the two methods. Surveys are the target of standardization processes at the European level (European Health Survey and Interview System). With some limitations, survey can be an interesting tool for specific RD indicators.

Surveillance systems: surveillance systems are in place in a very few settings and for certain conditions (e.g. British Pediatric Surveillance Unit: a card is sent to pediatricians each month to ask for any newly diagnosed cases of a few selected conditions; each condition runs for a few years and is then replaced by other priority conditions). Surveillance systems are very interesting tools of information and allow data collection of sentinel diseases and specific questions; applicability of such systems is limited to those healthcare systems in which the surveillance system is in place/can be implemented.

Literature: literature is a source of information accounting for e.g. diseases that are not classified, misclassified, or for extremely rare diseases, for which no system of data collection exists. Published case series, clinical trials, meta-analysis studies could be in certain cases the only available source of indicators of e.g. the effectiveness of a treatment/interventions toward patients' survival.

8. Conclusion

As a result of the Paris Workshop of 12 March, the WGHI proposed to investigate with Eurostat the feasibility of collecting mortality (death certificates) and hospital admission (hospital charts) data for some well defined RD. It is the opinion of the WGHI that the quality of RD indicator

data can improve (at the national and European levels) if they will be used on a more regular basis. Due to the readily mentioned classification problems, an approach toward the use of multiple sources of data is recommended (e.g. estimation of the prevalence of a RD using death certificates, registry and hospital charts). Concerning other indicators, an inventory of available data sources will be performed through use of different methods. One of the first initiatives will be a questionnaire directed to all known European scientific/clinical networks, to investigate which data, among those that are collected on a regular basis. This information could be useful in the development of RD indicators.

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ANNEX 1

List of European projects in the field of indicators

ECHI-European Community Health Indicators project (2001-2003): with the aim to provide common indicators for the European health information system, and give their operational definitions. A comprehensive list of around 400 indicators (long list) was produced throughout ECHI and ECHI-2. From this list of indicators, a so-called "shortlist" (approximately 80 indicators) was selected for priority implementation. Indicators are divided in classes/areas and classes/areas per disease, covering the most common diseases in the EU (<http://www.echim.org>)

ECHIM (2003-2008): this project continues the work of ECHI and ECHI-2. ECHIM acts as the scientific secretariat of the Working Party Indicators, comprising members from all Member States, leaders of five other Working Parties, project leaders of health indicator-relevant projects, and representatives from Eurostat, OECD and WHO. This should ensure that indicator development is in line with the needs of the European health information and knowledge system and that prerequisite for indicator implementation is created. Specific projects under the ECHIM umbrella develop indicators for : Mental health (MINDFUL and WP on Mental Health); Cancer (Eurochip and CAMON); Diabetes (EUPID); cardiovascular diseases (Eurociss); lung diseases (IMCA); Musculoskeletal disorders (MSD); oral health (EGOHID); injuries (WP accidents/injuries); perinatal health (Peristat); Child health (CHILD); reproductive health (Reprostat); health in intellectually disabled (POMONA); lifestyle indicators connected to cardiovascular diseases, diabetes, other major diseases (EHRM); Nutrition (EFCOSUM, Dafne and Public Health Nutrition); Environment and Health (ECOEHIS); Working Environment (Workhealth); health promotion (EUPHID).

OECD- Health Care Quality Indicators Project-HCQI: The objective of the OECD HCQI Project is to track health care quality by developing a set of indicators that are based on comparable data at international level (EU and other regions worldwide) and can be used to raise questions for further investigation on quality differences across countries. OECD has just released a data collection update report with data collected across 32 countries and a list of 19 indicators that seem to fit the purpose of making international comparisons on quality of health care.

ICHI - International Compendium of Health Indicators: ICHI is the collection of health indicators used by the international organizations WHO-Europe, OECD and the European Commission. The ICHI website allows the direct comparison of indicators and indicator definitions, and gives a full account of the ECHI indicator list proposed in the EU Public health Programme.

FEHES - Feasibility of a European Health Examination Survey: this project contributes to the development of a European Health Survey System by examining and analyzing the feasibility of carrying out a European Health Examination Survey (HES) or repeated HES in the EU Member States.

EUHSID (European Health Surveys Information) database: An inventory of nationally and internationally administered health interview and health examination surveys in: EU Member States, EFTA countries and some countries of other regions (USA, Canada and Australia). The database includes information on survey methodology, questionnaires, instruments and examination protocols, as well as recommendations.

ISARE - Health Indicators in the European Regions: A pilot project to test the feasibility of gathering health data at sub-national (regional) level within the EU. Over time, this project should lead to recommendations permitting easier integration of regional health data into the European databases.

EUPHIX - European Public Health Information, Knowledge & Data Management System: it is a prototype for a sustainable, web-based health information system for the EU, providing healthcare professionals, policy makers and other interested users with relevant, structured information on issues of public health across the EU, with particular relevance to health indicators.

EUROTHINE - Tackling Health Inequalities in Europe: The project aims at facilitating mutual learning by collecting and analyzing information from different European countries that will help policy-makers at the European and national level to develop rational strategies for tackling socio-economic inequalities in health.

EHEMU - European Health Expectancy Monitoring Unit: main aim of EHEMU is to provide a central facility for the coordinated analysis and synthesis of life and health expectancies to add the quality dimension to the quantity of life lived by the European populations, provide evidence of inequalities between Member States and highlight potential targets for public health strategies at both national and pan-European levels.

ANNEX 2

Definition of some proposed RD indicators, use, sources

A) Contribution of RD to morbidity/mortality

Prevalence

Definition: the number of persons affected by a certain disease in a given population (10,000;100,000) at a particular time. The current European definition of RD is based upon prevalence.

Use: surveillance of global health, particularly for chronic diseases. Establishing prevalence of RD is crucial to measure their impact as a public health issue; however, the sole use of prevalence can underestimate the burden of certain RD, e.g. conditions that are rapidly fatal. For these diseases, incidence is a better estimate. Differences in prevalence over time or between regions may reflect genetic or environmental differences, differences in diagnostic services, in quality of care, and in data collection methodology. Some important information in the field of RD can be generated by studying prevalence of a disease in certain age groups (e.g. perinatal) or in specific ethnic groups

Sources/feasibility: population-based registries, when available, are probably the best source for generating prevalence data, provided that the diseases are coded in the same way. Death certificates and hospital charts can be used, as already discussed in section 7, in combination with registry data. Alternative sources include literature data and scientific databases/clinical networks. Prevalence calculations can be tailored to the specific RD (e.g. prevalence rate at birth).

Incidence

Definition: the number of first events of a condition in a population (10.000; 100.000) during a specific time period. The period usually being one year, longer periods of observation might be necessary for conditions with a low rate of diagnosis (and with diagnosis delay), such as RD.

Use: due to the contribution of RD to children morbidity and mortality, incidence of RD in the perinatal period and the first years of life is very important information for policy-makers and the EU society at large. Incidence is a better epidemiological estimate than prevalence also in case of RD that is rapidly fatal, or acute/semi-acute, such as rare cancers. It is a very useful indicator to verify the effectiveness of prevention programs (e.g. prenatal screenings). The importance of incidence has been supported by the comments received during the public consultation on RD from several relevant stakeholders in the RD field. Note: due to the small numbers, an apparent “increase” in the incidence of some RD could result from improvement in the diagnosis and/or the classification of the disease.

Sources/feasibility: sources are registries and databases; information is reliable when registries are population-based. Incidence data in registries are often “cleaner” than prevalence data. As for prevalence, an integrated approach combining registries with hospital charts and mortality data can improve the validity of the information generated. Accredited genetic laboratories can be another possible source of information on incidence of genetic RD. For diseases for which data are not collected systematically, estimates of incidence can be made in some cases on the basis of the available literature data. The Orphanet report series of RD are important sources of data concerning RD incidence and prevalence.

Death rates (mortality)

Definition: the number of deaths in a certain population (100.000), by age groups and sex. Reduction of mortality is one of the most important targets of any policy intervention. Death rates are fundamental health indicators, even more so are age-specific mortality rates, especially in younger age groups. Infant and perinatal mortality are particularly relevant indicators for RD and different definitions can be used for these purposes.

Use: death rates for RD are to be monitored over time and between countries. They can be broken down in 5-year or 10-year age groups, according to the type of situation studied (e.g. rapid fatal diseases versus slow progressing diseases). In the RD field, an overview of mortality due to RD as a whole would increase the visibility of RD, show their impact on public health, and identify geographical inequalities and areas of improvement. Mortality data of diseases characterized by high/rapid mortality (e.g. cancers, neuromuscular diseases) or mortality in infancy/childhood are necessary to stimulate health policies for these specific diseases.

Sources/feasibility: Death certificates are the most important source of data, usually available in all nations/regions. National/regional RD registries usually contain mortality data. Multiple-cause-of-death records can be very useful in the field of RD. Characteristics and limits of death certificates as sources of data have been discussed in section 7. Collection of mortality data is ongoing for some RD within ad hoc projects/networks (e.g. rare cancers, congenital anomalies). Scientific/clinical databases can be used as source of mortality data for RD that are not properly coded, however they are biased by several limitations (e.g. non-population based data).

Hospital admissions/discharges

Definition: the number of hospital admissions in a certain population (e.g. 100.000) for a certain disease.

Use: hospital admission is a very important indicator to drive health policy interventions. Depending on the use for which this indicator is defined, single episodes of hospitalization or multi-stay rates can be used. In the field of RD, hospital admission/discharged certificates can be used to calculate incidence and prevalence, in this case, attention has to be paid to avoid data duplication/overlap with mortality data. Information on multi-stay and re-admission rates can provide strong evidence of the public health and economic impact of RD with high level of disability and elevated co-morbidity, and possible changes over time due to new treatments/interventions.

Sources/feasibility: Hospital admissions/discharges are administrative data that are being collected in all countries. However, hospital certificates are sensitive to classification problems and to local (national) application of classification systems. A systematic collection of hospitalization data for RD is not performed at European level at present. The WGHI encourages the use of hospital admission rates as indicators for RD, per se and as source of data about prevalence and incidence of RD.

In the area of RD contribution to morbidity/mortality, information over RD **contribution to mental/physical/neuro-sensory disabilities** and **contribution to transplantation** where also considered by the WGHI as valuable information tools, in which data collection is feasible. Disability registries exist for most invalidating conditions (e.g. deafness, blindness); and rehabilitation registries could be another source of data. Similarly, dedicated registries/lists could provide information over the contribution of RD transplantation.

The information generated from these indicators will show the impact of RD in individually affected patients and their families, and on healthcare expenditure.

Other indicators discussed in the area of RD contribution to morbidity/mortality were: health expectancy, quality of life, functional health. **Health expectancy** (e.g. DALY: disability adjusted life years; PYLL: potential years of life lost) is a very important indicator at European level. Feasibility and sources of this indicator in the RD field are at present not very clear. Health expectancy might be calculated for some RD, where valid incidence, survival and mortality data are recorded (e.g. rare cancers).

Similarly, data collected by clinical networks/databases can allow evaluation of quality of life over time for a very limited number of RD.

A) Socio-economic impact

Frequency of consanguineous marriages

Definition: in clinical genetics, a consanguineous marriage is defined as ‘a union between a couple related as second cousins or closer, equivalent to a coefficient of inbreeding in their progeny of $F \geq 0.0156$ ’. A common concern is that consanguinity leads to higher levels of mortality, morbidity in offspring due to the greater probability of inheriting a recessive gene. Consanguineous marriages in Europe are currently confined to particular ethnic groups.

Use: the WHO has recommended approaches to minimizing the negative effects of consanguinity on child health, i.e. the identification of families with a high risk of a genetic disease and the provision of prospective genetic counselling. Monitoring the frequency of consanguineous marriages can be used to understand geographical differences in prevalence/incidence of RD and to direct genetic counselling intervention.

Sources/feasibility: Genetic centres can usually provide data on the contribution of consanguinity to the occurrence of autosomal recessive diseases in the area they cover. Some voluntary centres may participate in monitoring this indicator over time.

In the area of socio-economic impact, the indicator ‘**impact on families (economic, social, and psychological)**’ has been discussed during the WGHI. More an information than an indicator per se, it is not easy in definition and quantification. However, information on the impact of RD on families is very important and lacking, therefore the WGHI stimulates efforts toward data collection in this field. The patients’ organization Eurordis performed a survey in several European countries to address this topic. This and similar initiatives can be the starting point for future assessment of the impact of RD on families.

The ‘**annual budget to cover orphan drugs**’, is regularly monitored by Eurordis.

C) (Availability of appropriate) Healthcare Services

Genetic testing: Laboratories accredited/certified/participating in EQA schemes

Definition: the number of laboratories for genetic testing accredited and certified at the EU level. In the past years, several efforts have been made to put in place networks for the assessment of quality standards of laboratories for genetic testing across Europe. In particular, EuroGentest and the EMQN (European Molecular Genetics Quality Network) have had an

important role in promoting and harmonizing quality testing and counselling in the field of rare genetic diseases.

Use: the number of laboratories accredited for genetic testing is an indicator of quality of health services and provision of care since it gives information about genetic diagnostic provision (of certified quality) with geographical differences and changes over time.

Sources/feasibility: Data on the number of laboratories can be obtained by the already mentioned networks of genetic laboratories, by several initiatives of the Commission and OECD, and by Orphanet. In the yearly reports, the number of laboratories can be divided in certified, accredited, and participating in EQA schemes.

RD for which a diagnostic testing exists

Definition: number of RD that can be diagnosed through a test. Diagnostic testing can be genetic, biochemical or metabolic.

Use: The availability of diagnostic tests for RD has an impact on diagnosis delay, and gives a better chance for early intervention, influencing health expectancy and epidemiological figures. Per se, this information tool reflects improvement in the knowledge of RD; inventories of the available diagnostic tests can be useful to identify areas not covered by ongoing research. The WGHI suggested monitoring **availability** of tests for RD (which test exists and in which countries are they available) and **accessibility**.

Sources: the existing tests and their availability per country can be regularly monitored by Orphanet, using as sources genetic labs and literature. For the monitoring of accessibility, an ad hoc survey is proposed by some WGHI members.

Prenatal diagnosis

Definition: the number of prenatal diagnostic tests for RD available/accessible; differences across countries and over time.

Use: prenatal diagnosis can have a very high impact on RD epidemiological figures. EUROCAT has recently conducted a survey of prenatal screening policies across Europe and their impact, reporting very different implementation of this type of screenings and related policies on the basis of cultural factors. It is useful to have information on screening policies and programs in EU countries and their impact on RD, informing national policy makers and the society at large of the quantitative impact of prenatal screening policies.

Sources: international dedicated registries (EUROCAT); national/regional birth registries.

Neonatal screening

Definition: number of neonatal screenings (metabolic/genetic) available/accessible; differences across countries and over time.

Use: The implementation of population or targeted screenings is affected by many issues, such as the availability of an effective treatment/intervention for those screened, the prevalence of the disease and its severity, and the choice/value that society attributes to the screening. It is important to identify where screenings can provide a high impact on mortality, health expectancy and other indicators. The implementation of screenings can obviously have a tremendous impact on RD for which treatments/prevention measures exist. If a screening is proven relevant, number of screenings implemented (i.e. that become standard assessments at birth/first days of life) can indicate the quality of health services, with geographical differences and over time.

Sources/feasibility: Data over the availability and validation of screening are available through dedicated sources such as the Human Genetic Society, which also releases recommendations and criteria for screening programs, information about availability of new screening methods is also provided by Orphanet. The number of screenings implemented in each country are easily accessible administrative data.

Diagnosis delay/age at diagnosis

Definition: an appropriate definition of age of diagnosis and diagnosis delay has to take into account diagnostic criteria for each disease and it can be difficult to calculate (delay) and/or to use as an indicator (age at diagnosis). Diagnosis delay refers to the interval between the first manifestations/lesions of a disease and the diagnosis (e.g. for breast cancer the interval between the first abnormal screen and the pathology confirmation of carcinoma).

Use: diagnosis delay is an indicator of the health service area. The delay in diagnosis is a very important prognostic parameter, and it can be crucial for diseases with severe outcomes which could be prevented by early intervention. Due to their situation of diagnostic complexity and scarcity of expertise, RD is particularly sensitive to diagnosis delays. Monitoring diagnosis delay across time and between countries is of great importance to evaluate progresses in the knowledge of RD, geographical inequalities which could be corrected through scientific networking/travelling of experts/training to primary care providers, areas to support with funding. Age at diagnosis can be used as a proxy (e.g. birth malformations that should be clinically recognized immediately after birth) and it is easier to monitor.

Sources/feasibility: Diagnosis delay can be difficult to assess and is sensitive to different definitions of first manifestations of the disease. Data on diagnosis delay/age at diagnosis are available in some registries, and some in dedicated international databases. Data of this kind are being collected by patients' organizations; survey can be an appropriate tool to investigate this indicator. Diagnostic/genetic laboratories can be a good source of delay/age at diagnosis data

New orphan medicinal product designations

Definition: the annual number of product that receive orphan medicinal designations by the European Medicine Agency (EMA).

Use: monitoring the number of medicines approved as 'orphan drugs'/year provides information about successful research and development in the field of treatments for RD, and the availability of new treatments at EU level. Policies to promote the creation of orphan drugs are being implemented in several EU countries (funds fore pre-clinical and clinical development) and the number of drugs produced/approved reflects also the efficacy of these policies.

Sources/feasibility: data are released and published regularly by the EMA.

Availability/accessibility of drugs with orphan designation

Definition: orphan drugs that reach the market once they have received authorization by EMA. Availability of/ accessibility to orphan drugs can have an impact on e.g. RD mortality, life expectancy, quality of life, just to mention a few.

Use: once new treatments for RD are approved by EMA, it is important to assess the real accessibility of orphan drugs for the patients, to identify the reasons of lack of availability (e.g. the new drug is not marketed) and accessibility (e.g. the new drug is not reimbursed) and of national/regional differences. Knowing about availability/accessibility of orphan drugs gives

information on local health service provisions and aims at solving inequalities in the access to orphan drugs.

Sources/feasibility: EMEA post marketing surveillance, Eurordis observatory on orphan drugs, Orphanet.

Number of patients' organizations

Definition: the number of patients' organizations and associations in Europe. This definition might include only those organizations with legal status or any organized activity by patients' groups. It has been proposed to evaluate also for which RD patients' organizations exist.

Use: Nowadays patient organizations play an active and instrumental role in determining RD public health and research policies, suggesting provision of services and providing feed-back on the quality of the services. The number of patients' associations is useful in determining the degree of social concern about RD.

Sources/feasibility: there are over 1 700 patients' organizations in Europe, with different legal status and geographical coverage. They are listed on the Orphanet web portal. Eurordis is also monitoring RD patients' organizations across Europe.

D) Information, research, technology development

Number of RD with a code/classification

Definition: Number of RD reported in an official classification system.

Use: monitoring the coding status of RD is at the basis of the generation of comparable data, and an information tool per se. This indicator is important for the recognition of RD as a health issue, to assure proper reporting mechanisms for RD, and can have great influence on health policies (e.g. reimbursement policies)

Sources/feasibility: the RDTF has a dedicated 'Working Group on Coding and Classification' and the chairman of the RDTF, Dr. Aymé, is collaborating with WHO in the revision of the ICD codes for RD to be implemented in the ICD 11. Therefore this indicator can be monitored; however, the next revision of ICD shall not be published any time soon. Initiatives are also recommended to assure proper classification of RD in other classification systems (SnowMed, MedDRA) and in assuring harmonized national transpositions of the international classifications.

Other indicators proposed by the WGHI in this area are: RD for which published practice guidelines are available; RD for which there is a registry with respective geographical coverage and RD for which there are ongoing clinical trials.

Regarding **guidelines for RD**, the level of evidence and the relevance of the sources can be assessed, and an ad hoc survey could be a possible instrument for data collection.

The **number of registries (and databases) dedicated to a specific RD** (or group of RD) is informative toward data collection initiatives, whether they come from public authorities (national/regional) or from scientific/clinical networks. Monitoring the number of registries, the diseases and the geographical areas covered by them is important to assess the status of information (data) collection in the field of RD, to avoid duplicate collections, and to identify which diseases are more 'neglected' among all RD. Monitoring the quality standards of registries and how many among the current registries are population-based is also important

information. A survey of RD registries across Europe is regularly conducted by Orphanet. Information about the **number of ongoing clinical trials for RD** in the EU can most likely be provided by the EMEA.

E) Equity, EU initiatives

Countries with specific funding processes and plans for RD

Definition: the number of MS with specific funding processes and plans for RD, in the field of research, in the field of information, in the field of healthcare (e.g. orphan drugs), in the field of testing.

Use: it is an indicator of healthcare intervention measures. In the presence of national action plans, particularly when developed according to common guidelines and criteria of best practice, the patients are guaranteed equal service and treatment all across Europe.

Sources/feasibility: data on national plans and funding processes are accessible through member states and EU sources. A specific project on national plans (Europlan) will be carried out by a group of members of The RDTF; collaboration with this study will be useful to the development of this indicator.

Number of European reference networks for RD

Definition: the concept of European reference networks (clinical/scientific) is quite new and still evolving. Criteria for European reference networks are indicated by the RDTF (WG on Networks of Reference) and the High Level Group on Health Services and Medical Care of the EC. Some networks have been funded in FP6 and FP7 to test and further develop the concept of European networks of reference.

Use: not an indicator but an information tool which testifies the progression of knowledge in the field of RD, the provision and quality of dedicated health services. From Reference Networks guidelines for best practices can be generated for the specific RD, transmission of knowledge and training of professionals can be organized.

Sources/feasibility: the number of European reference networks is up to now limited and it is accessible through the EC.

EU/national funding programs for RD research and public health

Definition: the number of funding programs for RD at EU and national level.

Use: informative over health policy measures and research. Suitable for analysis over time, indicates also the level of political interest and impact of RD.

Sources/feasibility: inventory of funding initiatives for RD is easy to realize, and dedicated web portals collect information about funding initiatives.

Courses, congresses and seminars on RD

Definition: the number of congresses seminars, courses in the field of RD.

Use: informative over increase and transmission of knowledge in the field of RD. Not an indicator, it is information worthwhile to be collected over time, to monitor the visibility of RD, the attention given to them by scientific societies and public institutions, and to identify possible geographical differences.

Sources/feasibility: For a systematic quantitative monitoring of this parameter, an inventory of the available sources of data (e.g. websites, scientific societies) can be useful.

ANNEX 3

List of participants to the workshop

Gemma Gatta (RARECARE)

Jean Donadieu (EURO HISTIO NET)

Han Trang (Centre of Reference for Ondine Syndrome)

S. Simpson (European Huntington's Disease Network) – 3,000 individual entries providing data on more than 12 HI.

Janos Sandor (Hungarian National Centre For Healthcare Audit and Improvement)

Laura Fregonese (Stichting Alpha1 International Registry)

M. Mazzacuto (Veneto Regional Registry of RD)

Anna Lisa Trama (Italian Center of Rare Diseases and EUROPLAN)

Arrigo Schieppati (Clinical Research Center for Rare Diseases)

Manuel Posada (Spanish Rare Disease Research Institute)

Antoni Montserrat (European Commission)

D. Schönfeld (German National Fabry Registry)

Yann Le Cam (EURORDIS)