Rare Diseases Task Force

HEALTH INDICATORS FOR RARE DISEASES:

I - CONCEPTUAL FRAMEWORK AND DEVELOPMENT OF INDICATORS FROM EXISTING SOURCES

Introduction

The present document is a synthesis of the previous Rare Diseases Task Force (RDTF) workshops on Indicators (30 January 2006, 12 March 2008 and the latest on 10 November 2009) and follows a report published in autumn 2008 of the RDTF entitled *"Health indicators for rare diseases: state of the art and future directions"*. The report of 2008 addressed the general need for health indicators for the field of rare diseases and explained the legal basis and the framework in virtue of which initiatives for the development of indicators might be possible for the first time in the history of rare disease health care. In preparing the field for indicators, an important role is played by integrated European rare diseases initiatives, for two main reasons: a) such initiatives stimulate public health plans and the creation of specific health services for rare diseases, and b) a European dimension is necessary for many indicators for rare diseases, due to the lack and geographical spread of data.

The correct form when quoting this document is:
"RDTF Report on Health indicators for rare diseases: I - Conceptual framework and development of indicators from existing sources", L. Fregonese, C. Rodwell, S. Aymé, April 2010
http://www.EUCERD.eu/upload/file/RDTFReportIndicatorsApril2010.pdf

Methodology and overview

Preliminary drafts of workshop reports are prepared before a yearly workshop dedicated to the topic. The final reports of the RDTF on the topic are a result of such workshops and discussions within the working group on health indicators of the RDTF, other RDTF members and experts consulted *ad hoc* on specific issues related to indicators for rare diseases. The present document is based on the discussion of the draft document *"Conceptual framework and working plan for the development of health indicators for rare diseases"* presented at the RDTF workshop on Indicators held on 10 November 2009 in Paris. The present document will be reviewed by the participants of the workshop and their comments will be taken into account in order to finalise this document - *"Conceptual framework and working plan for the development of health indicators for rare diseases: Conclusions from the RDTF Workshop (10/11/09)".*

The present report contains: a) a general methodological framework which highlights the topic of quality of data and fitness of data for the purpose of generating health indicators for rare diseases; b) examples and discussion of specific indicators that can be derived from existing sources; and c) conclusions from the workshop with strategies for the development of such indicators in the short to midterm.

The methodological framework addresses what *measuring health care* and *what measuring health (outcomes)* means and what the possibilities are in the field of rare diseases**.** What are the purposes of measuring health care and health in rare diseases? How can one measure health care/ health services and how to measure health/health status in the field of rare diseases? Two main types of indicators were discussed during the workshop (10/11/2009): indicators for health policies and initiatives on rare diseases at national and European level and their outcomes, and indicators of health status and health outcomes.

Concerning health policies and initiatives for rare diseases, some of the indicators identified by the Europlan project were presented during the Paris workshop and it was discussed how national plans already existing and/or which will be put in place could contribute to the development of health indicators for rare diseases. At European level, a selection of Orphanet data was presented - which were collected longitudinally and might allow country comparisons - and their potential of being developed into indicators were discussed.

Mortality is a key indicator in the field of health and particularly relevant in the case of rare diseases, many of which are fatal at very young age. The methodology and possibilities of valid mortality data collection in the field of rare diseases were addressed and data from the French mortality database were presented with selected results for cystic fibrosis, hemophilia A and B and sickle cell diseases.

The feasibility of indicators derived from data collected by registries dedicated to specific rare diseases was discussed, in the view of developing health outcomes indicators (other than mortality). Some potential indicators were presented during the workshop, based on the answers to a short questionnaire sent to some European registries in the month before the workshop (Annex 4), for Cushing's syndrome, spinocerebellar ataxia, Marfan disease and related disorders and alternating hemiplegia. Some other possible indicators were presented during the workshop for cystic fibrosis, Wilson's disease, congenital malformations and alpha1-antitrypsin deficiency.

Strategies and limitations were discussed regarding the development of indicators from national plans, Orphanet data, death certificates, and registries and the conclusion of such discussion are presented at the end of each chapter, with final general conclusions and strategy suggestions.

A strategy based on registries was viewed by all participants to the workshop as a resource-saving strategy which could help avoid duplicating effort. Future plans include questioning more registries about the possible indicators they can provide. Each disease for which registries with good quality data exist will be used as a 'sentinel disease'. Sentinel diseases are expected to allow the identification of trends, and should not be prioritised over other rare diseases as a result. Data derived from the registries will be analysed and will constitute the basis for a future platform of health indicators for rare diseases.

Development of indicators using the other sources addressed in the workshop will also be supported. In particular, the achievement of good quality mortality data for rare diseases in the different European countries will be stimulated, and a proposal for a European rare diseases' mortality registry should be put forward. Orphanet data will be further examined and propositions for definitions and formulations of indicators will be built, together in collaboration with national initiatives in order to develop over a short period of time health services indicators which are relevant in the field of rare diseases. Other possible sources, such as national genetics laboratories, will be explored.

A. Conceptual Framework for Health Indicators for Rare Diseases

1. The efforts of most countries to assess and 'incentivise' the performance of their health care systems have lead to the proliferation of indicators. To aid prioritisation and coherence of such indicators, conceptual frameworks are needed in order to ensure that the chosen indicators are valid measures for comparisons and that the main requirements and dimensions of the measurements are widely agreed and applied. This has been done for common diseases in several projects and by umbrella organisations such as the World Health Organisation (WHO) and the Organisation for the Economic Cooperation and Development (OECD), but does not exist for rare diseases. It has been seen as opportune to address in this workshop the building of a specific conceptual framework for rare diseases indicators.

2. The 2008 HIWG-RDTF Report defines the main purposes of indicators for rare diseases as agreed in the 2008 workshop. Such purposes are:

- *To measure RD globally and individually as a public health issue*

    - For visibility/advocacy

    - To identify targets of interventions

    - To allocate appropriate resources

- *To Enable surveillance of status and trends to*

    - Measure the impact of prevention, diagnosis/screening and care

    - Identify etiological and modifying factors

    - Analyse geographical differences and changes over time

    - Document influence of health policy measures

    - Guide of new research initiatives

3. Bearing these purposes in mind, we can identify the main areas/dimensions in relation to the current need of indicators for rare diseases:

- indicators to monitor the development of health policies and initiatives for rare diseases at national and at European level;
- indicators of health outcomes and health status;

Due to the geographical spread of rare diseases patients, it is likely that in many cases the collection of indicators will not be feasible in one single country or region and some indicators will be meaningful only when a broader (European) perspective is taken into account. Similarly, some indicators that would appear obvious (e.g. the number of centers of reference in a country) might be useless and have to be computed accordingly to the peculiar needs of the rare diseases situation (e.g. we might assume that measuring the 'number of patients followed by expert centres' would be a better indicator for small or very small countries, as this more accurately reflects the health care provided to the patients; however the number of centres might still be an important indicator for

bigger countries for health care planning purposes). In these cases a set of decisions will have to be made about the purposes and the applicability of the indicators.

4. In order to harmonise the development of different types of indicators from different sources, and to regularly discuss the coherence of indicators and data collection methodology with the main needs and problems of the rare diseases field, it might be opportune to create of an observatory of the working group on health indicators of the rare diseases task force with the aim of inventorying the present and future work in the field of rare diseases indicators and discuss all relevant conceptual and methodological issues related to the development of such indicators. It has been proposed by some of the participants to the workshop (10/11/09) that it would also be advantageous to involve health indicators experts from other fields on specific topics, such as e.g. quality of care.

Measuring health care

5. Health care is the combined functioning of public health and personal medical services, and a health care system is a set of agencies, facilities, and providers of care in a geographic area, i.e. the set of activities and actors with the aim of improving health through the provision of public health and personal medical services. Performance indicators have been developed by most countries to measure health care/health services and they serve two main purposes: to allow comparisons between countries and to formulate and monitor local health policies.

6. The recent recommendations from the European Council for the creation of specific national health policies for rare diseases, together with the large amount of information collected by a global observatory such as Orphanet, and by rare diseases registries, networks, patients' associations and projects, create for the first time the ground for the development of health care indicators in the field of rare diseases. Indicators that can be used for monitoring national and European initiatives for rare diseases are in most cases indicators of health services/health care performance.

7. Europlan is a three year project including several members of the RDTF, funded by the Public Health Programme of the European Union with the aim of developing guidance to facilitate the creation of national strategies/plans in line with the contents of the Council Recommendation on an action in the field of rare diseases approved by the European Council in June 2009. As plans and strategies need to be monitored, a work package of Europlan is dedicated to the development of indicators. A list of indicators has been discussed (the definitive list will be released at the end of the project) and indicators have been chosen so as to be sensitive to the recommended health policies, and adaptable to the different national realities.

8. In addition to the Europlan indicators measuring health care, other possible sources of indicators of quality of health care will be described in the next paragraphs, including: the database of Orphanet; administrative data and in particular data from death certificates; and data from registries specific for a single rare disease or a group of rare diseases. While all this sources have potential in the development of indicators for the quality of health care of rare diseases, registries are the only source with the potential of generating a large number of health status and health outcome indicators.

Measuring health

9. Health is a complex dimension, of which health care is only one determinant. As first identified in the Lalonde report of 1974, other factors such as nutrition, environment, life-style, poverty and social structure of society have been demonstrated to have a powerful effect on different health measures[1]. Some authors suggest breaking the definition of health into four elements: biology, environment, life style and health care organisation. Biology is an extremely important determinant in the case of rare diseases, the majority of which are of genetic origin.

10. As such, it might be opportune to keep in mind that indicators reflecting the performance of health care might inform about whether the health service works appropriately but often it might be difficult to connect the appropriate delivery of care with the outcome of the patient population (did the patients improve?). This is indeed going to be a challenge in the field of rare diseases, due to the paucity of standards of care and valid endpoints. In fact, establishing valid endpoints and clinical outcomes for rare diseases might be of great help for stirring health care, even with the difficulties of measuring such outcomes.

11. In the field of rare diseases we might be interested in measuring health using specific (health) indicators for many purposes, such as those judged as important in the 2008 RDTF HIWG report: to create visibility/advocacy, to identify targets of intervention, to identify etiological and modifying factors and to guide new research initiatives. Such purposes go beyond the evaluation of the performance of the health care services and require a different approach, such as the use of clinical outcomes. In this view, during the workshop (10/11/09) it has been agreed that even though health outcomes indicators might be difficult to implement, due to the lack of standards of care for many rare diseases, it is important to focus on such indicators and that comparison of outcome data by networking in Europe should be promoted.

12. Registries for specific rare diseases are very good potential data sources for the development of indicators to measure health status and health outcomes in rare diseases, offering at the present state some advantages on administrative data, such as the lack of codification biases and reduced costs of implementation. There are at present around 244 rare disease registries (dedicated to one specific rare disease or to a group of them) and 8 rare disease cohort registries in Europe[*] and some of them have been collecting data for several years. Substantial work has been carried out in the recent years towards establishing a methodology of data collection and ensuring the quality of registry data and such data are only seldom used for public health purposes. The role of registries as sources will be described in the next paragraphs.

---

[1] Lalonde M. A new perspective on the health of Canadians. A working document. Ottawa: Government of Canada 1974
[*] Source: Orphanet

B. Possible sources for health indicators

National plans

13. An example of possible indicators which could be developed at national level following the recommendations developed by Europlan in this field is given below (Figure 1).

Figure 1

Area to be explored	Aims	Actions	Indicators	Type of indicator	Answers
Global policy strategies on RD	To establish National/Regional plans and/or strategies on RD	Development of Regulations/Laws	Existence of regulations/laws that support the creation and development of a RD plan	Process	*Not existing, not clearly stated* □*Existing, clearly stated, partly implemented and enforced* □*Existing, clearly stated and substantially implemented and enforced*
			National/regional (percentage of regions)	Process	*Index based on the number of regions with a plan divided by total number of regions. A national plan will account for this index equal 100%*
		Establishment of Coordination mechanisms	Existence of a coordination mechanism	Process	*Not existing, not clearly stated* □*Existing, clearly stated, partly implemented and enforced* □*Existing, clearly stated and substantially implemented and enforced*
			Existence of an expert advisory committee	Process	*Exiting and meets regularly* □*Exists but partly functioning* □*Does not exist*
		Establishment of an external evaluation of the plan/strategy procedure	Existence of an external evaluation body/procedure	Process	*Number of meetings held by year*
		Degree of comprehensiveness	Number of priority areas included in the plan	Process	*Number ranging from 0 to 10*
		Establishing of a budget for developing the plan/strategy	Budget of plan/strategy	Process	*Overall budget allocated*

The indicators proposed in this table are process indicators, as they aim at monitoring the development and implementation of national strategies for rare diseases. Some health service outcome/health care indicators are also proposed in the work package, and are linked to the indicators proposed in the 2008 RDTF HIWG Report, such as 'the number of diseases included in the neonatal screening program', the 'proportion of laboratories having at least one diagnostic test validated by an external quality control', 'number of OD with EMEA market authorisation which are registered in the country', 'number of orphan drugs reimbursed 100%' among others. A list of the 2008 RDTF HIWG Report is included in Annex 1 and a discussion on process and outcome indicators is included in Annex 2 of the present report.

14. Amongst the indicators identified in the 2008 RDTF HIWG Report which can serve as health care measures, some have a European dimension rather than a national one, such as those related to the number and activities of European reference networks, or 'the number of registries for rare diseases', or the 'rare diseases for which a diagnostic test exist'. The same holds true for epidemiologic indicators which have been considered very important by the RDTF such as prevalence, incidence and mortality, indicators which are often difficult to collect for specific rare diseases at national level and which implementation will likely require the use of multiple data sources.

15. Most of the indicators which are being proposed by Europlan in order to assess national initiatives and national health care for rare diseases are not yet in place and adequate collection will only be possible in all countries when rare diseases initiatives and health care actions will exist (the European Union Council Recommendation on an action in the field of rare diseases sets this date at 2013) and provided that the countries start a reflection on the specific needs and problems related to performance (and others) indicators for rare diseases. However it is important to integrate the initiatives on health indicators for rare diseases of the single countries with the ongoing European initiatives and the work of the RDTF on this topic. Several members of health authorities of different European countries and members of Europlan involved in the development of national indicators participated at the workshop(10/11/09) and future plans in this direction were discussed, even though it will still require some time before national specific initiatives in this direction take place, with the exception of few countries.

Mortality data from death certificates

16. During the workshop (10/11/09) data from the French Institute for Public Health Surveillance (InVS) were presented about mortality from rare diseases. The work of the InVS on mortality data was aimed at improving the knowledge of rare diseases epidemiology by measuring mortality for some selected rare diseases. Diseases to be monitored were selected through prioritization criteria established through a Delphi method; however additional pragmatic criteria were whether a disease had a specific ICD-10 code and whether the disease was life-threatening disease. It is interesting to note that the feasibility, which in this case is represented by the availability of the code and in the case of registries by the existence of such registry for a specific disease, is a significant limiting factor in the development of health indicators for rare diseases, where coding and classification and data collection systems are much further behind such systems of more common diseases.

17. The annual number of deaths and mean age at death from the French mortality database were presented for cystic fibrosis, hemophilia A and B, and sickle cell disease, for the period 1981-2005. The methodology of data collection was illustrated, along with the difficulties linked to it.

The first problem, as already discussed in the 2008 RDTF HIWG Report, is the lack of proper coding, which renders many rare diseases invisible in administrative data collections. Currently 250 rare diseases do have a code but not all codes are correctly and widely used. In the Paris workshop more specific problems were addressed which can hinder the collection of mortality data for rare diseases, such as the fact that rare diseases may be registered as an associated condition leading to death. It was shown that for example hemophilia is frequently indicated as an associated and not as the underlying cause of death and that in the case of sickle cell disease only in 50% of cases the disease is listed amongst the underlying causes of death.

18. It has been noted that combining data from death certificates with hospital data may be necessary for some rare diseases in order to obtain complete and reliable mortality data. Such data mining work can be done only when specific programs (and specific funds) are allocated to it. Future plans of the group from the InVS are to study other rare diseases using the same criteria of prioritisation as the three diseases presented, using the national database of medical causes of death and the national hospital discharge database, and to make the results accessible on the website of the InVS.

19. It was agreed that mortality is an important indicator of the impact of rare diseases in general; it can guide health care planning and allow comparisons from country to country and over time for specific rare diseases, and is relevant for treatment outcomes. The selection of diseases to monitor and the methodology are crucial to ensure good quality and reliability of data. It was suggested to start with those diseases which have an ICD code (250 up to date) and to choose from these diseases those which are relevant to be monitored for public health surveillance. Prioritisation of the diseases

for public health surveillance should not be understood or translated as prioritisation of the selected diseases for care or research purposes. National plans and strategies for rare diseases should promote the use of coding by Orpha codes, which could be easily translatable into ICD-11 with a simple script, for national mortality databases and registries.

20. It was suggested by workshop participants that the French mortality database could be presented as a pilot to demonstrate the feasibility of mortality data for rare diseases and to forward a proposition for a European mortality registry, similarly to what has been already been done in other fields e.g. for the registry of mortality from injuries. European collaboration on rare diseases mortality data and exchange of experience about death certificates is needed. Experiences from mortality studies on single rare diseases by registries could also be useful as examples for methodology, such as e.g. a study performed by the UK registry on mucopolysaccaridoses which was cited during the workshop.

Orphanet data

21. The Orphanet database contains information about approximately 6,000 diseases, including data on prevalence. In addition it provides 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 rare diseases; a database of orphan drugs with their stage of development and availability in EU countries; and a range of other services or specific categories of stakeholders.

22. As such data from Orphanet was presented as possible sources for building indicators. In particular, indicators which could be relevant are the offer of genetic tests per country (over the total number of tests available for genetic diagnosis of rare diseases) and the number of genetic laboratories accredited by European quality schemes per country. Such indicators when formulated in a proper way would provide a measure of the quality of diagnosis of genetic rare diseases. During the workshop (10/11/09) some possible definitions and variants were discussed. Regarding genetic testing it was proposed to measure also collaboration for testing, which would reflect the provision of tests from a country to its population, independently from how many tests are implemented in the specific country. Regarding the genetic laboratories accredited by quality schemes, it has been noted by the participants to the workshop that besides the laboratories accredited by Eurogentest, which were presented from Orphanet, there are laboratories participating to other quality schemes, either national or international, and that the meaning of such indicator should be better specified. A possible formulation for an indicator of quality of genetic testing could therefore more generally refer to laboratories participating in at least one quality assessment scheme.

23. The topic of genetic counseling was introduced during the presentation of Orphanet and appropriate definitions of indicators in this area were discussed. It was argued that indicators based on numbers of genetic counseling units/clinics would not be applicable to all countries, as genetic counselling is organised in very different ways in different countries and there is a lack of gold standards. The aim of this indicator would be that of measuring services provided to the population in this area but dimensions should be better defined (number, quality of service, waiting lists).

24. Other information collected by the Orphanet database was presented, in relevant areas of monitoring, such as the availability of patients' organisations and of registries, the number of networks and/or the network's coverage, and orphan drugs. Possible indicators in these areas could be based on information such as the number of diseases covered by patients' organisations (Europe and/or country level), the number of rare diseases for which registries exist, and the number of European networks. Ways to study their impact of patients' organisations would be useful before or in parallel with the development of a specific indicator(s) in this area, and linked to this could be the specification of the type of services provided by the patients' associations and the budget. It has been noted that at present probably the most realisable and meaningful indicator in this area could be the number of diseases covered by patients' organisations, a number which can be monitored

over time, along with analysis of new alliances and networks. Trends in orphan drugs could be monitored through the number of rare diseases with at least one product in development/on the market, the number of ongoing clinical trials for rare diseases. Data from EMEA orphan drug designations and marketing authorisation should also be used by the RDTF in order to provide data on European trends in this field.

25. It was agreed that after reviewing the available Orphanet data, definitions, aims and dimensions of selected indicators should be studied, discussed in and built, in agreement with the general needs and conceptual formulations identified in the field of health indicators for rare diseases. Some indicators will benefit from interaction with the national plans and other national initiatives for rare diseases while a limited number of indicators might require only a European dimension/collection system,

Indicators from registries dedicated to a disease or a group of diseases

26. Registries dedicated to one or more rare diseases have data collection mechanisms in place and are therefore very important sources of epidemiology data for single diseases which are not being otherwise collected. As such, registries can provide a good picture of the disease in the community, highlighting problems and suggesting where there are population groups at high risk and where health services are most in need of improvement. The use of registry data minimises codification biases, since the patients enter the registry because the specific disease has been diagnosed. In general, if a registry is well established and clinical experts are involved in it, it can likely include a large part of the population of a country, or a region, affected by the specific disease. Many registries also report relevant health outcomes data. If the patterns are examined over time or within certain groups the information collected in the registry can be developed into indicators for evaluating changes in the disease and the effects of interventions, such as new treatments and health services/policies.

27. For a preliminary exploration of health indicators from registry data, a small pilot questionnaire was sent by e-mail prior to the workshop (10/11/09) to 40 coordinators of European global registries asking them which data, amongst the data currently collected by their registry, could be used as indicators, together with the justification for using such indicators, and the type of data. Some of the answers to this single question are reported below:

Figure 2. EUROSCA (European Integrated Project on Spinocerebellar Ataxia)

INDICATOR	JUSTIFICATION	TYPE OF DATA
Annual change SARA (Clinical Scale for the Assessment of Ataxia)	Validated clinical scale	Clinical scale
Annual change EQ5D	Validated indicator of health-related quality of life	Self-assessment scale

The EUROSCA registry includes 22 centres in 9 European countries *(Information from Prof. Klockgether)*

Figure 3. ERCUSYN (European Registry on Cushing's Syndrome)

INDICATOR	JUSTIFICATION	TYPE OF DATA
CushingQol score*	Disease-generated QoL questionnaire with 12 items, available in > 20 languages	Perceived health
24-hour urinary free cortisol excretion	Indicator of disease activity (elevated if hypercortisolism is present)	Biochemical parameter of disease activity
Midnight salivary cortisol measurement using Salivette[R] tube	Can be collected at home, is stable for several days , so can be mailed to the receiving lab	Biochemical indicator of presence of hypercortisolism, of high sensitivity and specificity, since it shows the lack of normal circadian midnight nadir of cortisol

The CushingQoL (quality of life) questionnaire is included in the Ercusyn database (European Registry on Cushing's syndrome) with participation from over 20 countries and more than 35 centres. In preliminary studies it has shown to be significantly correlated with hormonal parameters of disease activity. Data is collected longitudinally every year *(information from S. Webb)*.

Figure 4. Centre of Reference for Marfan disease and related disorders, Hospital Bichat, Paris

INDICATOR	JUSTIFICATION	TYPE OF DATA
Progression of aortic diameter	Marker of aortic risk, indication for surgery	Diameter in mm, need age height, weight and sex for interpretation
Number of aortic surgery	The main life threatening event other than aortic dissection	Ratio of the number of aortic surgery over number of patients followed
Number of aortic dissection	The main life threatening event, that medical car is supposed to prevent	Ratio of the number of aortic dissection over number of patients followed

(Information from Dr. Jondeau)

Figure 5. ENRAH (European Network on alternating hemiplegia)

INDICATOR	JUSTIFICATION	TYPE OF DATA
Incidence	A very rare disease , no proper estimation of incidence	Number of patients per new born in a (particular) year in a defined population
Age of diagnosis /delay in diagnosis	Under recognised and miss -diagnosed disease	The time between the appearance of first characteristic symptoms of the disease and the time of definitive diagnosis
Mortality	Number of anecdotal reports in the literature and parent's stories on sudden deaths	Number of deaths /registered patients

28. From these examples it appears that a great variety exists among the type of data that registries identify as important health indicators for the specific disease. Some answers are more focussed on epidemiologic data and others indicate clinical outcomes data (e.g. laboratory data, clinical events) and quality of life. Interestingly, quality of life has been given great relevance as an indicator for rare disease in the 2008 RDTF HIWG Report. The advantage of quality of life as a measurement is that it easily collected and it can be repeatedly evaluated also using the instrument of survey. However it is often not a well standardised outcome, therefore it is highly recommendable to take its measurement into account only when validated questionnaires/measurement tools exist.

In addition, during the workshop (10/11/09) representatives of some registries presented possible indicators for the diseases object of their registries.

EuroWilson

29. EuroWilson is the European database for Wilson's disease, an autosomal recessive disorder of copper metabolism causing hepatic disease, neurological complications and/or other abnormalities. Age of onset is variable but most often between childhood and young adulthood. The European clinical database was created in 2004 to order to collect data on the disease and design randomised controlled clinical trials. The registry, as for the majority of rare diseases registries, was not initially created for the purpose of developing epidemiologic data or health indicators; however a number of indicative measures have developed over time.

Information which can be derived from the Eurowilson database includes prevalence (cases/million population in 15 EU countries and 3 non-EU); age at diagnosis, and time from diagnosis to treatment. Age at diagnosis has been shown to be variable between countries, from a median of 8 years to over 25 years. The reasons for such differences can be partly explained by 1) in some countries the project had only paediatric coverage whilst in others there was a better coverage in neurology i.e. coverage of adult patients; 2) differences in the health care systems or 3) genetic differences.

Possible key indicators of quality of care which could be derived from Eurowilson data include: time from diagnosis to treatment; the number of laboratories accredited for genetic testing of Wilson's disease per country (which has been linked to a reduction in the error rate of diagnosis); and the rate of genetic testing in families of affected individuals, (family screening is extremely important for diagnosing and treating pre-symptomatic cases). Possible indicators relative to access to treatment and compliance with authoritative advice have also been described.

EUROCAT

30. EUROCAT is a large European Network of population-based registries for the epidemiologic surveillance of congenital anomalies, currently counting 41 member registries in 21 different countries. In 2006 it has been estimated that the coverage of EUROCAT is around 25% of European birth population. Several indicators have been suggested during the workshop (10/11/09) by the representative of EUROCAT, and in particular 5 of them are presently under discussion and a definition of such indicators has been formulated and is presently under discussion in the EUROCAT network.

The five main indicators are: 1) mortality burden, with a focus on perinatal mortality; 2) prenatal screening and termination of pregnancy for foetal anomaly (prevalence); 3) maternal age and

prenatal screening, defined as live born Down syndrome cases (per 1,000 births); 4) paediatric surgery; primary prevention by folic acid (measure: total prevalence of neural tube defects (per 1,000 births). For all indicators country comparisons are possible.

In addition, prevalence of 95 different congenital anomalies, resulting from grouping of ICD-10 codes, is already available in the EUROCAT website, by registry, year, and outcome of pregnancy (www.eurocat.ulster.ac.uk/pubdata).

EuroCareCF and European CF registry ECFS

31. The European coordination Action for Research in Cystic fibrosis EuroCare CF presented the demographics of cystic fibrosis computed on data from 35 countries for a total of more than 29,000 patients. The presentation was centred on what can constitute a simple, reliable, cost-effective marker of outcome in cystic fibrosis, a disease which is 'fit for purpose' as a test for the quality of care of a country because it is lethal unless it is treated. Possible indicators presented were age of diagnosis, age of death, and sex ratios. For each of these proposed indicators a methodology, definitions and possible biases were illustrated. Genotype as a confounder in the final data was mentioned and data were analysed separately for the most common (and most severe) mutation in Europe (F508del/F508del) and for the other mutations. Considerations were presented on age at diagnosis, how to compute and interpret it, and on diagnosis delay. Age at death data were also shown, together with survival curves for the UK population in two periods, 1994-1996 and 2000-2002. Expected age-banded prevalence of the disease by a certain age for a 90% ascertained group was interpreted as an indication of quality of care in single countries. Gender imbalance was described, with a disadvantage for females.

AIR: the Alpha 1 International Registry

32. The international registry for alpha-1 antitrypsin deficiency started collecting data in 1997 and counts at present data from 21 countries (EU and non-EU). Several mutations of the gene coding for alpha1-antitrypsin deficiency are known but not all of them lead to disease; as such it was decided that the registry should only contain data from the most severe mutations: ZZ, SZ and Null and rare variants.

The registry contains demographic data and several clinical/health outcomes data such as data of lung function and liver tests, computed tomography data, and quality of life. Information which can be used in order to create indicators from the AIR database include prevalence (cases/million European population and per country), and its changes over time, age of onset of symptoms and age at diagnosis, which can allow to calculate time from onset of symptoms to diagnosis.

Quality of life is measured using a validated questionnaire for obstructive pulmonary diseases, the St. George's questionnaire. Data on quality of life were analysed separately for the different genotypes, and country comparisons of quality of life can be easily computed from the available data. Among the clinical outcomes data, lung function data, and specifically the forced expiratory volume in the 1st second (FEV1) and gas transfer are the most relevant in order to evaluate the progression of the disease and the effects of interventions, including pharmacological treatments, (adequate) care and the impact of age at diagnosis on the severity of the disease.

C. Considerations and future plans on registries' data

33. Several considerations are important when evaluating the existing rare diseases registries' data in the light of the provision of health indicators, such as *representativeness of the real situation, geographical coverage, and intrinsic data quality.* Other issues relevant to indicators in general are, according to OECD: i) the importance of what is being measured; ii) the scientific soundness of the measure; iii) the feasibility/cost of obtaining the indicators. Annex 3 presents the OECD Criteria for selecting indicators of the quality of health care.

34. *Representativeness.* Among all the known registries in Europe, only few are population-based. A population-based registry aims at collecting all cases within a defined population according to a well-defined and standardised methodology for the collection of information and the diagnosis of the events/cases. When a registry is not population based, it is opportune that the use of the data as health indicators is carefully meditated and criteria and frameworks for the use of such data are defined.

Another issue related to the representativeness of registry data to the purpose of health indicators is the phenotype and spectrum of the disease reported by the registry. In the case of diseases with different levels of severity and developing slowly, only the most severe spectrum of the disease might be represented by the registry, therefore masking the real situation of the disease for epidemiology and for public health purposes.

35. *Geographic coverage*. In common diseases, indicators are chosen so to give a picture of a whole country even though several exceptions can be made. For example OECD has considered acceptable to use also data that represent only one particular region or area in a country. Does it make sense to look at 'national representativeness' of the data in the field of rare diseases? When national representativeness is not possible, what are the criteria to define when the geographical coverage is acceptable? Would it be necessary to study specific measures of geographic coverage for rare diseases?

36. *The quality of data* is a very important issue in registries, independently from whether the data will be used for the generation of indicators. A large amount of work on registries has been done by the RDTF in the past years and it should be taken into account when considering the use of registry data. Issues related to quality which might be of particular relevance for the development of health indicators are e.g. bias from diagnostic practices and changes in coding systems, the impact of new diagnostic tools and re-definition of events; data comparability within the register (i.e. different sub-populations, different time points, etc); data comparability with other registries within and between countries.

37. Linked to quality for the provision of health indicators is also the continuity of data collection. To be used as indicators, data has to be collected longitudinally. In the current situation many registries are not in the position to assure a regular data collection over time, because of lack or cessation of funding. In addition, different health care systems across European countries and different privacy regulations might cause differences between countries in terms of patients lost to follow-up.

38. As registries already have data collection methods in place and data sets available, it was agreed during the workshop (10/11/09) that this data should be looked at in priority. A strategy based on registries has been viewed by all participants to the workshop as resource-saving and avoiding efforts duplication. The first step will be to extend to other registries the pilot work started before the workshop. The methodology will replicate the one of this pilot, with a single question sent to registries with quality control mechanisms in place. Each registry will be asked to provide relevant indicators, with justification for proposing/using such indicators and the type of data (Annex 1).

39. The diseases object of such registries will be as such used as 'sentinel diseases' to build the case and show the feasibility of indicators in the field of rare diseases. The results will produce a variety of indicators for a variety of diseases, but these indicators would still allow the identification of trends. Registries linked to reference centres could also be questioned in selected cases. It is also hoped that showing the usefulness of registry data for public health purposes will stimulate other registries to make their data suitable for being used as indicators and other diseases to put data collection systems in place.

It was remarked during the workshop (10/11/09) that such a choice has not to be translated in a prioritisation for public health purposes of the sentinel diseases over those diseases for which data collection is not existing or not adequate. Rather, it is hoped that showing the added value of registries for public health purposes will stimulate more registries to improve data quality and more diseases to develop data collection systems. To this purpose, during the workshop it was suggested to study incentives for rarer diseases in order to help starting data collection.

40. The issues of quality of the data and fitness for purpose have been extensively discussed during the workshop (10/11/09). In particular it was proposed that even though the data with quality controls will be the first ones to be used, it will be worthwhile to explore also the possibilities and methods to use 'less-good quality' data, semi-quantitative and qualitative data. A panel of members of the RDTF working group on health indicators should carry the task to further develop the conceptual framework for indicators for rare diseases working through regular 2-3 times a year meetings, in collaboration with external experts when necessary.

41. In this direction, a detailed questionnaire was discussed in the workshop (10/11/09), which could be used to evaluate the characteristics of all existing registries for rare diseases, the type and the aims of data they collect, the quality of such data, the geographical coverage. Such questionnaire will allow getting a better knowledge of the currently existing registries for rare diseases and their potential of developing indicators for rare diseases. The questionnaire is presented at Annex 5.

42. It has been noted that most of the existing registries have not been created with the purpose of measuring indicators for rare diseases; however in the past years some of these registries have 'professionalised' the data collection to such extent that they are nowadays able to provide data suitable for this purpose. Strategies to improve and standardise data collection have been discussed during the workshop (10/11/09), such as: link the activity of registers to the centres of expertise; harmonise data collection formats; choose a limited number of indicator fields per registry and clearly define their purpose.

D. General conclusions of the workshop (10/11/09)

43. After discussing existing possible sources of health indicators for rare diseases, a strategy based on registries has been viewed by all participants to the workshop (10/11/09) as resource-saving and avoiding efforts duplication. Development of indicators by the other sources addressed in the workshop will also be supported and pursued.

44. Each disease for which registries with good quality data exist will be used as 'sentinel disease' for the purpose of monitoring rare diseases with indicators. Those registries will be asked to provide relevant indicators, with justification for proposing/using such indicators and the type of data (Annex 4).

45. Sentinel diseases are expected to allow the identification of trends, and should not be prioritised over other rare diseases as a result. Data derived from the registries will be analysed and will constitute the basis for a future platform of health indicators for rare diseases.

46. Discussion will be continued on the conceptual framework of health indicators for rare diseases, and on important issues related to the use of registry data for this purpose such as quality of the data, continuity, representativeness and geographic coverage. It is envisaged that common standards for registries would be needed to this purpose, and work in this direction should be done, together with stimulating more registries to see the value of developing data for public health use. In this view, a very detailed questionnaire might be used to explore the characteristics of registries other than the sentinel ones (Annex 5).

47. A good quality of administrative mortality data for rare diseases in as many as possible European countries is a clear goal for the coming years. Selection of the rare diseases to monitor for mortality should be based on the availability of ICD codes before other criteria. Among the remaining criteria, early mortality has been considered the most important. It was suggested that the methodology of the French rare diseases' mortality database could be seen as a pilot and shared with other European countries, and a proposition for a European mortality registry for rare diseases should be put forward.

48. Orphanet data will be further examined and propositions for definitions and formulations of indicators will be built; at the same time collaboration with existing and/or potential systems of health indicators at national level will be stimulated and supported. The use of Orpha codes at national level would facilitate the development of specific indicators for rare diseases in the framework of national plans and national administrative data, and the creation of a common European background for indicators, since Orpha codes will be easily translatable in the upcoming ICD-11.

49. Other possible sources of indicators for rare diseases will be explored, amongst them data from expert laboratories have been considered promising, in particular for data on prevalence, incidence, age of diagnosis (as an example, national genetic references laboratories in UK were mentioned). Academic registries could be another possible source.

49. Independently from the sources, it is advisable to start with indicators which are relevant but also simple and delivering clear messages to patients, health professionals and policy makers. This will help to 'build the case' of health indicators for rare diseases, and to show the feasibility. In addition, possible/expected changes in the indicators should be properly defined.

50. A sub-group of the RDTF working group on health indicators could meet regularly (e.g. 2-3 times a year) in order to discuss methodological issues related to indicators, and the work in process. Such work would take advantage from ad hoc collaboration with international renowned experts in the field of indicators in general in some specific occasions.

51. The Paris workshop was concluded by a round of closing comments from the participants; all comments have been taken into account and incorporated in the present report.

ANNEX 1

RELEVANT INDICATORS IN THE FIELD OF RARE DISEASES AS FROM THE 2008 RDTF WORKSHOP ON HEALTH INDICATORS

A list of potential relevant indicators in the field of rare diseases has been finalized during the HIWG Workshop of 2008 and presented in the 2008 RDTF HIWG report.

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)

The aforementioned indicators are in some cases very well established epidemiological measures, such as incidence and prevalence, other might be relatively easy to calculate, such as the number of registries, the number of orphan drugs, the number of reference centres or networks, provided that the indicators satisfies some fundamental criteria which will be

discussed further in this draft. Other items of the list of the 2008 RDTF HIWG report are not immediately translatable in indicators, such as where the item is defined as 'contribution to' and 'impact on'. In these cases the most appropriate indicators should be chosen for the computation of the desired information.

ANNEX 2

STRUCTURE, PROCESS AND OUTCOME INDICATORS
# (Revision from literature)

One widely accepted and useful method for categorising indicators of health care is the approach first conceptualised by Donabedian that described indicators as being structure, process or outcome in nature.

Structure indicators are indicators of the structural and fundamental characteristics of health care (e.g. whether doctors are suitably qualified and whether hospitals are appropriately equipped). They may represent necessary conditions for the delivery of quality health care but they are not sufficient, as their assessment does not ensure that appropriate processes are carried out or that satisfactory outcomes are achieved by the health system.

Process indicators measure how appropriately (or inappropriately) health care is delivered to the relevant population at risk (with appropriateness based on clinical evidence of the effectiveness of the process concerned and 'consistent with current professional knowledge'). Examples of such indicators are e.g. whether children are immunised appropriately.

Outcome indicators aim at measuring health changes and as such they measure something which is important in its own right. In fact it is interesting to know that changes in the health status of a patient population happen, and are different from country to country, even without knowing why. When outcome indicators want to be used as measures of health care performance, attention has to be paid as whether there is sufficient evidence that quality of care makes an independent contribution to the outcome, as the outcome is likely to be influenced by other factors but quality of care.

The figure presents a schema of the three types of indicators:
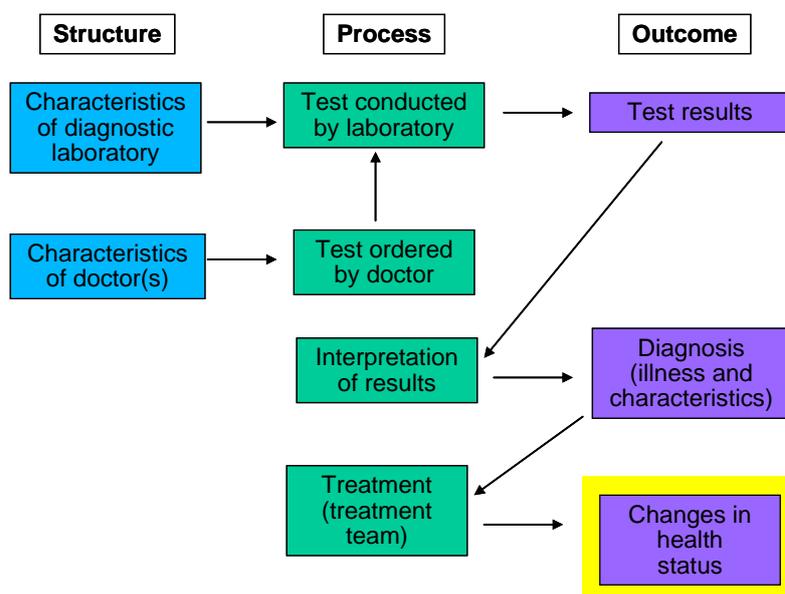
Process and outcome indicators are not in competition with each other but there are some circumstances in which one type of measure is likely to be more useful than the other. It is therefore important to be aware of the strength and weaknesses of the two types of indicators in order to be able to choose how and when to use them

The advantage of *process indicators* is that they are more sensitive to differences in the quality of care, and they are therefore widely used as direct measures of quality. Obviously, it is easier to measure whether children have been immunised properly (process) than whether the vaccination has resulted in protection (outcome), as the outcome will depend not only from whether the vaccination has been administered appropriately but also from the immune response of each child, from the strength of the infectious agent and from other potential variables. However, there are some concerns about the degree to which such measures are related to clinical outcomes, as health is not only determined by health care

but also by biological, lifestyle and environmental factors. In addition, process indicators are considered to be more vulnerable to gaming than outcome measures.

Health outcome indicators have been suggested to be relevant when a broader perspective is desirable, as they reflect a variety of factors, some related to health care and some not and, as already mentioned, they can provide information which is relevant *per se* and as such sufficient e.g. to inspire or guide health policies. Outcome measures have several limitations when used as indicators of health care performance, due to the confounding of the factors other than health care which influence the outcome. Such factors, when identifiable, should be appropriately accounted for by risk adjustment. It has to be acknowledged that the clinical data with the detail necessary for comprehensive risk adjustment is often lacking, especially at the international level. Nevertheless, an effort should be made to adjust indicators to the degree possible and the limitations should be kept in mind when interpreting results (OECD).

Sources

- OECD HEALTH WORKING PAPERS NO. 23. HEALTH CARE QUALITY INDICATORS PROJECT CONCEPTUAL FRAMEWORK PAPER Edward Kelley and Jeremy Hurst. DELSA/HEA/WD/HWP(2006)3

- Mant J. Process vs. outcome indicators in the assessment of quality of the health care. International Journal for Quality in the Health Care 2001; 13:475-480

- Donabedian A: An Introduction to Quality Assurance in Health Care. Oxford: Oxford University Press; 2003

- Donabedian A: Explorations in Quality Assessment and Monitoring. Vol. 1. The Definition of Quality and Approaches to its Assessment. Ann Arbor: Health Administration Press; 1980.

ANNEX 3

OECD CRITERIA FOR SELECTING INDICATORS OF THE QUALITY OF HEALTH CARE

OECD HEALTH WORKING PAPERS NO. 23. HEALTH CARE QUALITY INDICATORS PROJECT CONCEPTUAL FRAMEWORK PAPER Edward Kelley and Jeremy Hurst. DELSA/HEA/WD/HWP(2006)3

1. Importance of what is being measured

• *Impact of disease or risk on health and on health expenditure.* What is the impact on health and on health expenditure associated with each disease, risk or client group? To help understand these impacts, the OECD has prepared a list of conditions with the highest costs, morbidity, and mortality. Preferably, the measure will address areas in which there is a clear gap between the actual and potential levels of health that can be influenced by improvements in the quality of care.

• *Policy importance.* Are policy makers and consumers concerned about this disease or risk group area?

• *Susceptibility to being influenced by the health care system.* Can the health care system meaningfully address this disease area or problem? The measure should reflect an aspect of health that can be influenced by the health care system as it exists or as it is envisioned. That is, policy makers can take specific actions (generally at the structural or process level) to improve health care in that area and, ultimately, health status. Injuries caused by automobile accidents, for example, are the leading cause of death among young adults, but most remedies (for example, changing car design or reducing the speed limit) lie outside the influence of the health care sector.

2. ***Scientific soundness*** of the measure

• *Validity.* Does the measure actually measure what it is intended to measure? The measure should make sense logically and clinically (face validity); it should correlate well with other measures of the same aspects of the quality of care (construct validity) and should capture meaningful aspects of the quality of care (content validity) (Carmines and Zeller, 1991; Nunnally, 1978). In general, measures should be linked to significant processes or outcomes of care as demonstrated by scientific studies. For example, the provision of selected screening tests in a timely manner is a process measure of quality that has construct validity when the screening is linked to earlier detection of disease and a better prognosis or outcome. Outcome measures should be examined for validity in a similar manner.

• *Reliability.* Does the measure provide stable results across various populations and circumstances? The measure should produce consistent results when repeated in the same populations and settings, even when assessed by different people or at different times. Measure variability should result from changes in the subject of measurement rather than from artefacts of measurement (for example, a change in the definition of the measure or, for rare events, restricted sample size or small numbers of cases). This aspect is particularly important for periodic data collection. Most measures will have to be repeated every year, and any changes in the measure should reflect a true change in quality.

• *Explicitness of the evidence base.* Is there scientific evidence available to support the measure? There should be a clearly documented scientific foundation for the measure in the literature. An explicit evidence base could also mean that there is some other specific, formal process by which the measure has been accepted as a valid marker for quality, such as review by an expert panel.

3. ***Feasibility*** of obtaining internationally comparable data for the measure
• *Existence of prototypes*. Is the measure in use?

- Availability of internationally-comparable data across countries. Can internationally-comparable information needed for the measure be collected for sufficient countries in the time frame required? At one extreme, a few indicators of the technical quality of health care can already be found for most countries in *OECD Health Data*. At the other extreme, there will be many potential indicators for which few if any countries could provide any data in the foreseeable future. In between these extremes, there are likely to be some indicators for which data would be readily available at national level for a significant group of countries, but with variations in the precise definitions of numerators and denominators. There are likely to be other indicators for which national data has not yet been assembled (say, from local or clinical databases) and which could be put together according to a common definition only with considerable effort.

• *Cost or burden of measurement.* How much will it cost to collect the data needed for the measure?

Note of OECD
This list has been modified directly from the report "Envisioning the National Health Care Quality Report" by the US Institute of Medicine (Hurtado MP, Swift EK, and Corrigan JM, eds., (Washington: National Academy Press, 2001)). References Nunnally, J.C. 1978. Psychometric Theory. 2nd ed. New York: McGraw-Hill.
Carmines EG and Zeller RA. 1991. Reliability and Validity Assessment. Newbury Park, Calif.: Sage Publications.

ANNEX 4

EU RARE DISEASES TASK FORCE
Working Group on Health Indicators

QUESTIONNAIRE FOR THE DEVELOPMENT OF HEALTH INDICATORS FROM REGISTRIES DEDICATED TO RARE DISEASES

Dear Madam/Sir,

You are the coordinator of a registry in the field of Rare Diseases. The European Commission is committed to monitor the effects of National and European policies in the field of health care, and the EU Rare Diseases Task Force has the task to analyze the possibilities of developing health indicators for rare diseases.

We believe that registries are in a favorable position for developing such indicators and would like to ask your participation in setting up a system for rare diseases' indicators in the EU.

Participation in the development of European system of indicators for rare diseases is a great opportunity to valorize the data collected by your registry, and it will demonstrate the public health role and importance of registries, which is at present underestimated.

The results of collection of indicators for rare diseases from registries will be published in an official report of the EU rare diseases task force (becoming the EU rare diseases expert committee as of May 2010), giving visibility to registries' data collection.

We wonder if you could identify one of more indicators from your current data which could serve as an indicator over time and across countries. An ideal indicator has to be robust and unambiguous; this may restrict your choice. The most interesting indicators are those liable to change over time in function with the policies in force.

Among the data you collect, could you suggest relevant indicators for the specific disease/group of diseases? (Please provide justification(s) per each indicator-see examples in the Annex at the end of next page)

INDICATOR	JUSTIFICATION	TYPE OF DATA

Would you be available to produce such indicators longitudinally? (e.g. once a year or at another suitable time-interval for each indicator). Please indicate if yes, no, and reasons for your choice.

_____

_____

_____

_____

Annex

Examples of possible indicators

The following are just examples and do suggest a specific way of answering.

INDICATOR	JUSTIFICATION	TYPE OF DATA
Annual change FEV1	A validated indicator of progression in obstructive lung disease.	Functional (lung function); % of predicted value
Perinatal mortality (for a specific RD)	RD 'x' is characterized by elevated perinatal mortality; area of monitoring and action.	Epidemiology; N perinatal deaths/1000 total births /(year)

ANNEX 5

EU RARE DISEASES TASK FORCE
Working Group on Health Indicators

QUESTIONNAIRE FOR EVALUATING REGISTRIES AS SOURCES OF HEALTH INDICATORS DATA

Health care planning requires the use of indicators, objective measures that enable the description of the situation of a certain disease (health status of the patients, health outcomes, health services provided for the disease) and the changes in such situation as a result of health care interventions.

The European Commission is committed to monitor the effects of National and European policies in the field of health care, and the EU Rare Diseases Task Force has the task to analyze the possibilities of developing health indicators for rare diseases. We believe that registries for specific rare diseases are in a unique position as potential data sources for the development of indicators; however such potential is up to now largely unexplored.

We would like to ask your participation in exploring the characteristics of registries for rare diseases in Europe, with the aim of setting up a system for rare diseases' indicators in the EU. Participation in such project is a way of valorizing your data, showing that your registry may be useful in monitoring effects of health care policies and interventions in your country and at international level, and supporting the role of registries as public health tools.

The following questionnaire investigates objectives, methods and type of data collected by registries for rare diseases in Europe. The majority of existing registries have not been created with the purpose of producing health indicators; however in the years data collection has become more and more professional and many registries have put in place or are starting data quality control measures. The present questionnaire aims at gaining an overview on which type of data are available in Europe to the purpose of developing health indicators for rare diseases, and for which diseases.
The results of the analysis of the answered questionnaires will be made public through an official report from the EU rare diseases task force, giving visibility to the involved registries and hopefully further stimulating data collection for rare diseases.

In case of questions on finalities and methodology of the questionnaire please contact:

Laura Fregonese
Centre Hospitalier Universitaire Vaudois
Lausanne, Switzerland
Leiden University Medical Centre
Leiden, Netherlands
+41 21 3140544
+31 6 255 10721

laurafregonese@gmail.com

SECTION 1- OBJECTIVES AND METHODS OF DATA COLLECTION

1- When was the database/registry established? _____ (please indicate year)

2- Is data collection by your registry: (please put a cross after the applicable answer)

a) Cross-sectional _____

b) Longitudinal _____

c) Both _____

3- How many years of data are retrievable from your registry? _____

4- Which were the purposes for starting data collection? (please rate from 0 to 4)

- Epidemiology _____
- Repository of cases for *ad hoc* studies (e.g. case control) _____
- Clinical research (clinical trials, diagnostic tools) _____
- Basic research (e.g. mechanisms of the disease, genetics) _____
- collection of biological material _____
- Planning and evaluation of specific health service s _____
- Other (please specify) _____

_____

5- Is data collection population-based?

(please circle/highlight the applicable answer) YES/NO/NA

6- Which is the geographic coverage of your data? (e.g. regional, national, number of EU countries, etcetera; please specify and if possible give details)

_____

_____

7- Who contributes data? How many sources?

_____

_____

_____

8- Is there a control mechanism on the sources and the quality of the data?

(please circle/highlight the applicable answer)   YES/NO/NA

9- If YES, what is your quality control mechanism?

_____

_____

10- On the basis of your quality control, would you consider the quality of the data you are currently collecting as:

(please circle/highlight the applicable answer)   GOLD/SILVER/BRONZE/NA

11- Is your registry consented? (Is consensus obtained before inserting patient's data in the registry/ (please circle/highlight the applicable answer)   YES/NO/NA

12- Are data in your registry (please put a cross after the applicable answer)

    a) Anonymous (consented)_____

    b) Anonymous (non consented)_____

    c) Patients are identifiable_____

SECTION 2- TYPE OF DATA

13- Does your registry collect: (please put a cross after the applicable answer)

a) Only demographic data   _____

b) Demographic and clinical data   _____

Which type of data do you collect?

14- Demographics and Epidemiology

1- Demographic patients' data	YES/NO/NA
2- Demographic family data	YES/NO/NA
3- Consanguinity	YES/NO/NA
4- Onset of symptoms	YES/NO/NA
5- Diagnostic method	YES/NO/NA
6- Date of clinical diagnosis	YES/NO/NA
7- Date of genetic diagnosis	YES/NO/NA
8- Hospital admissions	YES/NO/NA
9- Date of death	YES/NO/NA
9- Time from diagnosis to treatment	YES/NO/NA
10- Other	

_____

_____

15- Health and functional status

Degree of severity of the disease   YES/NO/NA

Please indicate if you use or not a validated scale and if yes,

which_____

_____

Global health status   YES/NO/NA

Please indicate if you use or not a validated scale and if yes,

which_____

_____

Comorbidities   YES/NO/NA

Quality of life   YES/NO/NA

Please indicate if you use or not a validated scale and if yes,

which_____

_____

Functional status/disability   YES/NO/NA

Please   indicate   if   you   use   or   not   a   validated   scale   and   if   yes,

which_____

_____

Working status
YES/NO/NA

Social life/activity   YES/NO/NA

Other (please specify)

_____

_____

16- Treatment

   1- Orphan drugs   YES/NO/NA

   2- Non-Orphan drugs   YES/NO/NA

   3- Non-pharmacological treatment (e.g. devices, diet, moisturisers)   YES/NO/NA
   If YES, please specify_____

   4- Transplantation (either solid or bone-marrow)   YES/NO/NA

   5- Treatment outcome   YES/NO/NA

17- Access to treatment

    1- Reimbursement   YES/NO/NA

    2- Clinical trials   YES/NO/NA

    3- Compassionate use   YES/NO/NA

    4- Other_____

_____

SECTION 3- HEALTH INDICATORS

Besides the data that we indicated in the previous sections, you registry might contain data and measures that are specific for the single RD/group of RD (e.g. specific clinical/radiologic/functional data). Among the data collected in your registry, can you indicate which ones are the most relevant for the specific RD/group of RD and can be used as health indicators for the disease? (Please provide justification(s) per each indicator)

INDICATOR	JUSTIFICATION	TYPE OF DATA

Thank you for taking the time to answer these questions!

The RDTF Working Group on Health Indicators

Appendix 1

Examples of answers to section 3

INDICATOR	JUSTIFICATION	TYPE OF DATA
Annual change FEV1	A validated indicator of progression in obstructive lung disease.	Functional (lung function); % of predicted value
Perinatal mortality (for a specific RD)	RD 'x' is characterized by elevated perinatal mortality- area of monitoring and action.	Epidemiology; N perinatal deaths for 1000 total births /(year)

ANNEX 6
QUESTIONS RAISED AT THE WORKSHOP ON INDICATORS (10/11/2009)

1) Questionnaire on registries as sources of health indicators

- Evaluation of registries and sources (ongoing): after the Paris workshop the questionnaire for registries will be revised accordingly to the received comments and distributed to the European RD registry.

- Which registry dimension do we want to evaluate with this exercise:
  - Only population based
  - Also non-population based when collecting 'sufficient' data (definition of sufficient?)
  - European coverage
  - National coverage

- Are the questions presented in a way that is easy to interpret/score?

- How do we think we can use indicators derived by registries? (for which purposes?)

- Any other suggestions?

2) Creation of a conceptual framework for national and European indicators for rare diseases

- How can we appropriately measure health care in RD?

- How can we appropriately measure health status?

- Can we imagine health care indicators which are much related to the clinical outcome and

- How can we identify signals related to the RD field in general as opposed to signals for single RD?

- Does it make sense to look at 'national representativeness' of the data in the field of RD? When national representativeness is not possible, which are the criteria to define when the geographical coverage is acceptable? Would it be necessary to study specific measures of geographic coverage for rare diseases?

3) Way forward

- Will it be useful to choose sentinel diseases in EU to evaluate the feasibility of health indicators for rare diseases? Can we choose such sentinel diseases on the base of the availability of data?

- Role of the HIWG as observatory for rare disease indicators

ANNEX 7

LIST OF PARTICIPANTS – RDTF INDICATORS WORKSHOP
PARIS, 10 NOVEMBER 2009

Adamski, Jakub *(Ministry of Health – Poland)*
Aymé, Ségolène *(Leader of the RDTF, Director of Orphanet - France)*
Donadieu, Jean *(CHU Hôpital d'Enfants Armand-Trousseau –France)*
Fregonese, Laura *(Leiden University Medical Centre – the Netherlands)*
Gomes, Eugenia *(InVS – France)*
Handley, Olivia *(European Huntington's Disease Network – UK)*
Jansen, Herwig *(Scientific Institute of Public Health – Belgium)*
Jessop, Edmund *(National Commissiong Group NHS - UK)*
Kent, Alastair *(Genetic Interest Group – UK)*
Khoshnood, Babak *(INSERM – France)*
Kremp- Roussey, Odile *(Ministère de la Santé et des Sports – France)*
Landais, Paul *(Hôpital Necker Enfants Malades – France)*
Lavery, Christine *(MPS Society – UK)*
Le Cam, Yann *(Eurordis – France)*
Le Henanff, Guillaume *(Ministère de la Santé et des Sports – France)*
Macek, Milan *(Charles University Prague: 2nd Medical School – Czech Republic)*
Mehta, Anil *(University of Dundee – UK)*
Miteva, Tsonka *(Information Centre for Rare Diseases and Orphan Drugs – Bulgaria)*
Nourissier, Christel *(Eurordis – France)*
Ostli, Elin *(Norwegian Directorate of Health – Norway)*
Palau, Francesc *(CIBERER – Spain)*
Parker, Samantha *(Orphan Europe – France)*
Posada, Manuel *(Rare Diseases Research Institute:- Instituto de salud Carlos III – Spain)*
Rodwell, Charlotte *(RDTF Scientific Secretariat - France)*
Sandor, Janos *(University of Debrecen Faculty of Public Health - Hungary)*
Stokke, Bodil *(Norwegian Directorate of Health – Norway)*
Stuhrmann – Spangenberg, Manfred *(Medical School Hannover, Institute of Human Genetics – Germany)*
Suzan, Florence *(InVS – France)*
Van Weely, Sonja *(Dutch Steering Committee on Orphan Drugs – The Netherlands)*
Vittozzi, Luciano *(Istituto Superiore di Sanità – Centro Nazionale Malattie Rare – Italy)*
Voigtländer, Till *(Medical University Vienna – Austria)*

Observers:

Ashton, Charlotte *(National Commissiong Group NHS - UK)*
Guesdon, Benjamin *(Orphanet - France)*
Jovanovic, Mariana *(Orphanet - France)*
Taylor, Louise *(Orphanet - France)*