QUESTION 1: IS THE CURRENT EU DEFINITION OF A RARE DISEASE SATISFACTORY?

The definition currently indicated in the Community Action Programme on rare diseases is based on a prevalence criterion, i.e. below the limit of 5 cases per 10.000 inhabitants. Compared to other countries, only for the EU legislation the criterion of prevalence is constant over time. This characteristic is particularly important in relation to the fact that it doesn't consider a standard number of cases, based on estimates that may vary over time. To date, the prevalence figures of rare diseases in the general population are too preliminary or limited to specific geographical context or age ranges. The evaluation on whether the definition is too wide depends on the availability of figures deriving from area-based monitoring systems. This precondition is difficult to be pursued on a wide scale in a short period of time. In our opinion, the definition currently used should be kept as the reference definition, since changing it know would create confusion for the already developed or currently developing monitoring systems. Only when reliable figures on the fraction of the EU population affected by a rare disease will be available, we will be able to judge if the definition is too wide, too narrow or adequate. The existing Registries focused on a specific disease, or on a group of diseases, despite their importance in improving the knowledge on specific disorders, are of limited usefulness from a health care planning point of view. To properly determine the impact of rare disorders at a population level, area-based surveillance systems are needed, monitoring not the single conditions but the whole group of rare disorders. A common definition of rare disease is of crucial importance to set up these monitoring systems.

Beside the prevalence criterion, the definition of a rare disease could be based also on other criteria, such as for example the complexity of care required, although in this phase adding extra criteria could be in some way confusing. The *a priori* definition of the burden required in terms of care results a difficult task, because also within the same disease different patients may experience different profiles of complexity of care. Moreover, besides the complexity of care, the status of rare implies in itself a possible difficult diagnosis, which requires the existence of defined Centres providing a prompt and correct *depistage*.

QUESTION 2: DO YOU AGREE THAT THERE IS A PRESSING NEED TO IMPROVE CODING AND CLASSIFICATION IN THIS AREA?

The International Classification of Diseases in its different releases represents the basis for mortality and morbidity statistics, comparable at an international level.

Ameliorating the coding and classification system for rare diseases is urgent for different reasons. First of all, we need estimates of the number of affected patients, starting from current statistics, based on ICD-coding. To date, prevalence data deriving from area-based monitoring systems are available only for few selected specific contexts. Increasing the sensitivity in registering patients with a rare disease using the ICD-coding would provide useful data also for the areas where the population monitoring is particularly difficult to be realized. Moreover, the obtainable figures would be useful not only to estimate the prevalence of the disease, but also to be able to trace the patient "care pathway" throughout the Services (hospital and community-based).

In order to improve the power of current statistics for detecting rare diseases, we have to rethink both the coding and the classification systems. For the coding system, a strategy has to be taken to define in some way the specific rare disease within a general non-specific code. Besides the coding, we have to think about the classification logic. To date, ICD releases have a systems-centred classification that complicates the coding of rare multi-systemic diseases and lacks in indicating some nosological categories, i.e. mitochondrial diseases, currently scattered in several different ICD categories.

QUESTION 3: CAN A EUROPEAN INVENTORY OF RARE DISEASES HELP YOUR NATIONAL/REGIONAL SYSTEM TO BETTER DEAL WITH RD?

Undoubtedly, an inventory of rare diseases would be extremely useful to guarantee visibility to patients and to improve access to benefits, if provided by specific laws. The goal of creating a single list of rare diseases is consequent to the adoption of a shared and common definition of a rare disease, at least at EU level. Moreover, the list should be based on a shared classification logic. Clinicians do not always agree on the terms to be used to define or on the classification criteria to be used to group different diseases; even if a consensus exists, the research advances and the production of new scientific knowledge may add elements that modify the classification and the grouping criteria. This element arises the problem of the updating of the list, particularly if some Member States will refer to the list to provide benefits for affected patients or for the organization of interventions programmes.

QUESTION 4: SHOULD THE EUROPEAN REFERENCE NETWORKS PRIVILEGE THE TRANSFER OF KNOWLEDGE? THE MOBILITY OF PATIENTS? BOTH? HOW?

In the field of rare disorders and in general great impulse should be given to the process of transfer of knowledge. This is one of the topics of translational research, which refers to the transfer of new advances, mechanisms and techniques coming from basic science research into new approaches for prevention, diagnosis and treatment of diseases. The process of transfer should ensure that new treatments actually reach the patients for whom they are implemented. The transfer refers also to the dissemination of best practices, leading to a better coordination of systems of care. Rare diseases represent a paradigm of how both these two aspects of translational research should be contemporarily implemented by the reference centres and stakeholders. There is an urgent need to promote and support the development not only of new drugs, but also of medical aids, devices, and every kind of intervention aimed at improving the survival and the quality of life of patients; nevertheless rare diseases patients could at the same time benefit from the betterment of the health care system in improving access to already existing treatment options reducing the fragmentation of the health care pathways. The aim is to disseminate information in the health services network.
Finally, the mobility of patients should be limited to those situations really necessitating referral to distant clinical centres, avoiding any possible additional burden for the patient and his/her family.

QUESTION 5: SHOULD ON-LINE AND ELECTRONIC TOOLS BE IMPLEMENTED IN THIS AREA?

The development of *on-line and electronic tools* represents a priority action in the field of rare diseases. These actions are strongly linked to the need of filling in the gap existing between what is known by the patients and what is available in terms of information on the disease and its natural history, on the reference centres, and the available treatments and benefits.

Since 2002 in the Veneto Region a unique computerized monitoring system allowing diagnosis recording, exemption leading to benefits' entitlement and cases' enrolment in the Registry for rare disorders was implemented. In 2004, a strategic agreement in the field of rare diseases was signed by the Veneto Region, Friuli Venezia Giulia Region and the Autonomous Provinces of Trento and Bolzano, in order to create a "Wide Area", with common reference centres, completely covered by the same monitoring system, the one already in use in Veneto Region. Strategic points of the agreement are the implementation of common health plans to support training, information and research programmes in the field of RD. The system guarantees the free mobility of the patients in this Wide Area, at the same time simplifying the procedures to achieve the benefits provided by law. This system is used also in the neighbouring Region of Emilia-Romagna and is going to be used in Liguria Region. This system connects all the identified centres of reference, all the health districts and the local pharmaceutical services. The patient enters the surveillance system after a specific diagnosis of rare disease has been made, which is followed by the exemption issued by the local health districts. In this way the patient can receive the benefits provided by law. All the information is automatically managed by the same system, providing direct services to the patients as well as a real time link among all the health and social Services of the Region. Being part of the existing Health Services network represents the plus value of the monitoring system. This system is structured in order to connect the vertical networks of the reference centres and the horizontal networks of primary care services, located in the community where persons live.

The monitoring system is an informative tool directly delivering services to the patients, planned and implemented, both in contents and architecture, in order to simplify the pathways of patients in obtaining the benefits issued by the law. The information and the technical solutions implemented represent the glue connecting, around the patient, all the different actors that in different phases and with different roles are involved in the *prise en charge* processes.

Therapeutic protocols elaborated by the reference centres are accessible and shared through the informative system. In our experience this on-line tool is very useful to promote the shift from the process of collecting information to the elaboration of consensus guidelines, improving clinical practice standardization and progressively increasing the quality of the interventions.

QUESTION 6: WHAT CAN BE DONE TO FURTHER IMPROVE ACCESS TO QUALITY TESTING FOR RD?

On what attains the tests, we need to differentiate among the availability of tests that result efficient in the general population and those referring to subgroups of patients, the amelioration of which requires basic and translational research, availability of well-qualified bio-banks, and the accessibility to theoretically available tests.

The accessibility depends both on the presence of high quality of labs in all countries, and on the conditions of reimbursement or payment of the tests. From this point of view, an harmonization among different EU countries on what attains the access to available diagnostic techniques should be encouraged. A strategic role is played by the creation of monitoring systems of the diagnostic quality of the labs and of the testing procedures, through area-based systems implemented in the general population.

QUESTION 7: DO YOU SEE A MAJOR NEED IN HAVING AN EU LEVEL ASSESSMENT OF POTENTIAL POPULATION SCREENING FOR RD?

There is certainly the need to have an evaluation of potential population screening for RD at EU level. In general, rare diseases have to comply with the criteria adopted by the WHO and National Health and Medical Research Council (NHMRC) when planning screening programs. The main issues are the characteristics of the test itself, in particular sensitivity and specificity, and the provision of treatments for the screened condition. To set up a screening programme there should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment. Nevertheless, screening programs are proposed also for conditions that don't actually meet these criteria. Furthermore, another issue is the lack of agreed evidence-based policies defining which individuals should be offered treatment and which is the appropriate treatment to be offered. If these criteria are not fulfilled, the proposal of screening programs should not be considered as an health care intervention, but it could be more correctly evaluated in the context of research projects.

QUESTION 8: DO YOU ENVISAGE THE SOLUTION TO THE ORPHAN DRUGS ACCESSIBILITY PROBLEM ON A NATIONAL SCALE OR ON AN EU SCALE?

The accessibility to the orphan drugs depends on the organization of the health care system of each EU country, either based on a universalistic system or on private insurances. In any case in our opinion, the implementation of post-marketing monitoring systems could strongly support the sustainability of the health systems as well as drugs' accessibility in the medium and long-term period, allowing also the modification of the drugs' market prices, according to their real utilization both at a national and at a EU level.

QUESTION 9: SHOULD THE EU HAVE AN ORPHAN REGULATION ON MEDICAL DEVICES AND DIAGNOSTICS?

The medical devices are more oriented to answer to a health care problem rather than being developed for a specific disease. For this reason, the same medical device could be useful for disabilities determined by both rare and non rare diseases.

If regulations would be issued in order to provide incentives for the development of such devices, this would be very useful, but it could also affect the accessibility of the patients to the devices due to the possible non sustainability of the system, as can happen in the case of OMP.

Moreover, the application for the orphan designation could lead to the forced fragmentation of subgroups within the same disease entity, amplifying the *salami slicing* phenomenon.

We think that any regulation should take into consideration both the need for research and development boosting and the need to guarantee the economical sustainability of the system.

QUESTION 10: WHAT KIND OF SPECIALISED SOCIAL AND EDUCATIONAL SERVICES FOR RD PATIENTS AND THEIR FAMILIES SHOULD BE RECOMMENDED AT EU LEVEL AND AT NATIONAL LEVEL?

Persons with rare diseases commonly face problems in obtaining benefits, even when they are clearly provided by law, for example social and economic support as a consequence of disabilities related to the rare condition. The difficulty experienced by rare diseases patients is even more considerable than the one experienced by other patients, due to the fact that it is more complex to evaluate the consequences produced by the disease on the affected person. The lack of knowledge that characterizes these conditions refers both to the disease itself and to the disability profile produced. Further elements of complexity are interindividual variability and a scarce knowledge of natural histories. As for all patients, but especially for patients affected by a rare disease, the disease involves all the dimensions of the human being, i.e. social life, relationships, activities of daily living. As a consequence, many Institutions, Services and professionals, not necessarily directly devoted to health care, result involved in the process of *prise en charge.*

The *prise en charge*, in order to support the best possible development, social inclusion and non discrimination, has to take into consideration other important aspects such as access to education or to work. In this direction, laws protecting the rights of patients and their families have been issued at national levels. Nevertheless, these rights and the modalities for accessing them are commonly poorly known, paradoxically mainly to entitled persons.

Even when realized, these interventions too often stand apart from all the other care activities and interventions carried out in different contexts or by different Services. In this framework, a key role can be played by the Health Care Plan, an instrument shaped on the patient and tailored on his/her health care needs, the use of which should be strongly promoted. This plan has to be dynamic, ensuring continuity among vertical (Reference Centres) and horizontal networks (community Services), and all the other institutions and Services involved in the process of *prise en charge* of the person affected by a rare disease.

QUESTION 11: WHAT MODEL OF GOVERNANCE AND OF FUNDING SCHEME WOULD BE APPROPRIATE FOR REGISTRIES, DATABASES AND BIOBANKS?

Different elements result crucial in the implementation and governance of data-bases, registries and bio-banks. First of all, data-bases linked to public institutions are needed, independent from companies, possibly area-based in order to estimate the impact of the monitored phenomena at a population level. The monitored area has to be wide enough to catch even rare events.

A two ways and strong link between who delivers the health care services, in the framework of an integrated *prise en charge*, and who issues the health care policies and is responsible for resources allocation should exist. The registries need to be placed at the same level of the health care government, who is on turn placed differently at a national and regional level in Europe.

Looking at the dimension of the monitored population, at EU level can be in some way confusing to speak of national and regional registries, since some regions account for a population that is larger than the one of some nations. It would be therefore more appropriate to refer to the monitored population rather than to the national or regional level. The link between the different levels of monitoring it is for sure essential and can be realized through the progressive identification of common rules in the definition of what to monitor and how to monitor.

All the same, the funding system, in order to be appropriate, will have to consider mostly the specific elements defined above rather than the definition of the national or regional level of the monitoring itself.

QUESTION 12: HOW DO YOU SEE THE ROLE OF PARTNERS (INDUSTRY AND CHARITIES) IN AN EU ACTION ON RARE DISEASES? WHAT MODEL WOULD BE THE MOST APPROPRIATE?

Both industry and charities play a key role in the development of research activities and of new tools for the treatment and prevention of rare diseases. In this context, the consortium model involving public institutions carrying out research activities, companies, health care networks and charities could represent the best solution in order to guarantee the multiplicity of the point of views and consequently the balance between choices, actions, economic and technological allocated resources and coherence between objectives and the weight of the patients' real needs.

QUESTION 13: DO YOU AGREE WITH THE IDEA OF HAVING ACTION PLANS? IF YES SHOULD IT BE AT NATIONAL OR REGIONAL LEVEL IN YOUR COUNTRY?

The fact that health care planning strategies can be carried out in the framework of a specific Plan for rare diseases is a key-point for the development of coordinated and effective interventions. National and regional or interregional Plans are not mutually exclusive. The unavoidable condition for their success is that they are shaped according to the existing health care organization. National Plans can differ in form from one country to another, reflecting the heterogeneity of national health systems. Similarly, different Regions within a country can benefit from the development of tailored plans, not disregarding the specificity of the regional health care organization and considering what has been already implemented.

QUESTION 14: DO YOU CONSIDER IT NECESSARY TO ESTABLISH A NEW EUROPEAN AGENCY ON RD AND TO LAUNCH A FEASIBILITY STUDY IN 2009?

If the European Agency will be structured as a flexible tool aimed at simplifying and promoting activities and scientific research, it will be more than welcome. If its creation will determine the making of a complex and expensive entity, this fact could constitute an element of rigidity of the system and a potential obstacle to the development of new initiatives and timely solutions to new requests.