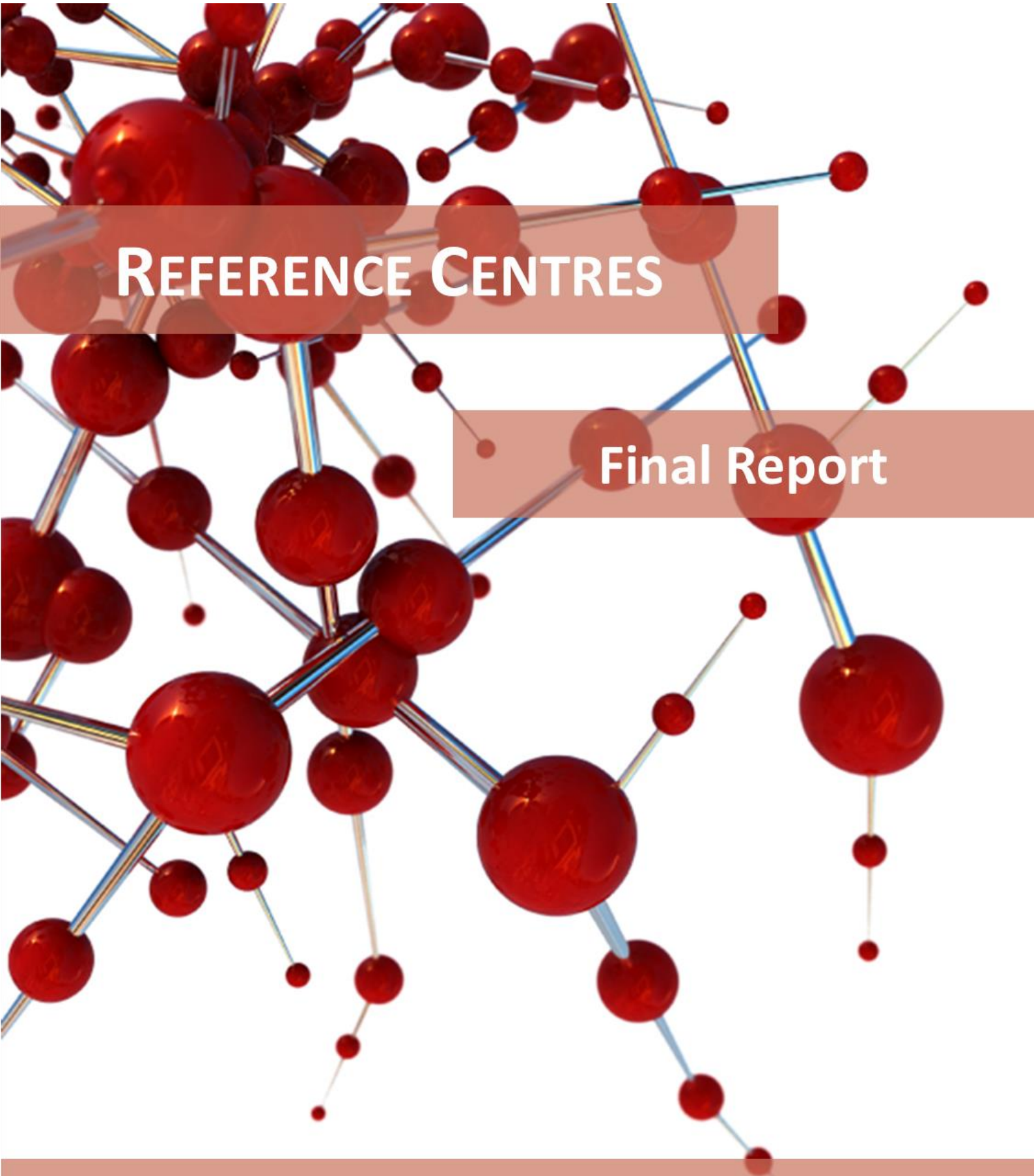

REFERENCE CENTRES

Final Report

Work Group created by Order n.º 4319/2013 of his Excellency The Joint Secretary of State of the Minister of Health, published in the Official Journal Series II, 59 (2013-03-25)

GOVERNO DE PORTUGAL

MINISTÉRIO DA SAÚDE

REFERENCE CENTRES – Final Report

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ABBREVIATIONS, ACRONYMS AND SYMBOLS

ACSS	Central Administration of the Health System, I.P.
CA	Affiliated Centre
CCTDLS	Coordinating Commission of Treatment of Lysosomal Storage Diseases
CED	High Differentiation Centre
CNA	National Associated Centre
CPLP	Community of Portuguese Speaking Countries
CR	Reference Centre
CT	Treatment Centre
DGS	General Directorate of Health
DLS	Lysosomal Storage Diseases
E.P.E.	Corporate Public Entity
EUCERD	European Union Committee of Experts on Rare Diseases
EUSOMA	European Society of Breast Cancer Specialists
GT	Work Group
GTRH	Technical Group for Hospital Reform
IPO	Portuguese Institute of Oncology
IRODaT	International Registry of Organ Donation and Transplantation
PNS	National Health Plan
RER	European Reference Network
RRH	Hospital Reference Network
SNS	National Health Service

CONVENTIONAL SIGNS

Cf.	See
e.g.	For example
n.a.	Not applicable
pmh	Per million inhabitants
T	Trimester

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EXECUTIVE SUMMARY

The concept of “Reference Centre” has been gradually adopted by a group of reference texts in spite of the absence of any profound and conclusive reflection about its meaning, and about its implications towards the organization of the health system.

This concept has become priority within the current Government, namely in the context of health, being clearly identified in the report from the Technical Group for Hospital Reform as a strategic and essential priority for modernization and consolidation of both the speciality and quality defence within hospital units rendering health care.

Having the Government assumed the aforementioned priority, a Work Group was established, pursuant to the **Order of the Deputy Secretary of State of the Ministry of Health No. 4319/2013**, of 15 of March, issued on the Official Journal, series II, No. 59, of 25 of March, to put forward a definition for Reference Centre, establish the criteria for the Ministry of Health to identify and characterise Reference Centres, propose a model for implementation and financing, as well as to plan out how such a concept would become a part of the Portuguese Hospital Network and the European Reference Network.

As a consequence of Directive 2011/24/EU, of 9 of March, of the European Parliament and of the Council on the application of patients' rights in cross-border healthcare, the Portuguese health system needs to officially identify and recognise highly specialised clinical centres, named “Reference Centres”, that may come to join future the European Reference Networks envisioned in the aforementioned Directive.

In fact, Directive 2011/24/EU, of 9 of March, of the European Parliament and of the Council is bringing up a European movement for the creation of healthcare reference networks aiming to explore the possibilities found in the cooperation between the Member States of the European Union.

One may then find a recent history sustaining, solidly and rationally, the decision to go forward with the creation of reference centres.

The future role of the reference centres in these European networks will be carried out voluntarily, so long as the conditions and criteria previously defined by the legislation of the country in which these are located are met, as well as those to be defined by decision of the European Commission.

It is therefore predicted that this European offer of reference centres interlinked as a network will lead to higher quality, efficiency and safety, promoting economies of scale that will further improve efficiency and maximise the cost-effectiveness of healthcare practices.

The transposition of Directive 2011/24/EU of 9 of March, of the European Parliament and of the Council to national legislation will require a formal definition of the concept of reference centre, the establishment of national criteria for its creation and the development of mechanisms in order for them to be officially recognised by the Ministry of Health.

Portugal must carry on with the development of this process of creation and recognition of reference centres, otherwise being subjected to being deprived from the future European Reference Networks, which would lead an isolated national health system and the loss of reputation and competitiveness compared to the remaining Member States, becoming solely an exporter of complex clinical situations instead of, in a similar manner, constituting an attraction for the patients within the European area in specific, specialised fields.

Directive 2011/24/EU, of 9 of March, of the European Parliament and of the Council states that the European Commission must support the development of the European Reference Networks of the reference centres in each Member State. In compliance with Directive 2011/24/EU, of 9 of March, of the European Parliament and of the Council, the European Commission has created a Committee on cross-border healthcare and named a group of European experts for the European Reference Networks within this field, where the Portuguese Ministry of Health also takes part. As such, it will be the responsibility of the European Commission to define the model of governance of the European Reference Networks, and the responsibility of the Member States, as stated in the norms approved, to register the rules in the national legislation.

Thus, and in line with Directive 2011/24/EU, of 9 of March, of the European Parliament and of the Council, this report proposes that a **reference centre be defined as a unit providing healthcare, with verified technical knowledge on the administration of high quality health care to patients in certain clinical situations, which require resources on a large scale, as well as knowledge and expertise, due to the low prevalence rate of a condition, and how complex the diagnostic or treatment procedures are and the high costs of these same situations.**

As a result, a reference centre must be composed of expert and highly qualified multidisciplinary teams and specialised medical facilities and equipment, in order to ensure that the healthcare practices administered keeping the highest quality standards in mind and in accordance with the evidence available and the specific recommendations of the scientific community.

The identification and official recognition, on a national level, of each reference centre must be encouraged by the need to have highly specialised healthcare practices concentrated or centralised in a limited number of services and hospitals and the determination to improve the expertise on a clinical level and regarding research on diagnostics and specific treatment.

This report describes the general criteria a national reference centre must abide by for it to be officially recognised by the Ministry of Health and lists the criteria for the European Reference Networks the European Commission is still discussing.

For the assessment and national recognition proposal of future reference centres, this report proposes the establishment of three main fields of analysis: Classification Commission, Technical Specifications Experts Group and Technical Commission for Assessment.

The Work Group also proposes a deployment model and the principles underlying the financing and contract terms of the reference centres.

In regards to the financing and contract terms, it must be emphasised that, although the work group understands by general principles that the reference centres must follow the coverage capacity on a national level and that only the entities chosen to provide certain healthcare practices must be

contracted/financed to do so, the payment methods to be established mu be studied per case, depending on its suitability to the field/procedure/pathology considered.

The European Commission is currently drawing up a final concept for European Reference Network as a network of reference centres connecting a special concentration of resources, knowledge, skills and expertise, based on the performance within healthcare of high quality standards, accessible and cost-effective, making it possible to make not only training and research a point of attraction, but also the circulation of information, knowledge and assessment.

Portugal's engagement in these European networks will promote the inclusion of the Portuguese Health System in healthcare procedures of high quality on a European scale, making it necessary carry onto the adaptation of national legislation and the development of a course of action and thus keeping in mind Directive 2011/24/EU, of 9 of March, of the European Council and of the Council.

The Work Group presents a group of areas of priority that should make up the first areas to introduce Reference Centres in Portugal. Focus on solid organ transplants, oesophageal cancer, stomach cancer, rectum cancer, liver and bile duct cancer, pancreatic cancer, testicular cancer, breast cancer, melanoma, and childhood cancer. Haemophilia and inherited metabolism disorders also to be noted. In regards to procedures, the Work Group presents the proposal of creating the first Reference Centres on haemodynamics and intervention cardiology.

The Work Group presents a number of recommendations understood to be vital to the pursuit of the creation of Reference Centres in Portugal.

1 INTRODUCTION

The health systems o the European Union are a crucial component of social protection, contributing to social cohesion, social justice and the sustainable development of the Union, therefore constituting a large part of the services of general interest.

As acknowledged by the European Council in its conclusions in June 2006, on values and principles shared by the health systems of the European Union, there is a number of common functioning principles, shared by the health systems across the Union. These functioning principles are necessary to guarantee the patients' trust on cross-border healthcare, contributing to the free movement of patients across European territory.

Similarly to what is seen in other European countries after a community procedure that culminated in the publishing on the Official Journey of the European Union, in April 2011, of Directive 2011/24/EU, of 9 of March, of the European Parliament and of the Council on the application of patients' rights in cross-border healthcare, from here on referred to as Directive, the Portuguese health system needs to identify, officially recognise, and map centres of high specialisation in the administration of healthcare. This process must be modelled in order to adapt cases, skills and resources based on general and specific criteria that will allow for more effective assignment of these factors based on the hierarchy of skills and its articulation with the Hospital Reference Networks (RRH), with similar national, European and international centres.

In fact, as ordered by the Directive, a European movement, in which Portugal is taking part, has been set in motion for the creation of the European Reference Networks (RER) between healthcare practitioners and the Reference Centres (CR) of the Member States, exploring the possibilities of European cooperation in highly specialised healthcare fields.

The RER will rely on the voluntary participation of the specialised centres that satisfy the conditions and criteria defined by the European Commission and in the legislation of the Member State where these are located, therefore contributing to the improvement of diagnostics and high quality healthcare

practices, efficient and accessible to patients whose clinical condition requires a special concentration of specialised medical knowledge.

Portugal was then encouraged, together with other Member States, to connect highly specialised centres in its national territory for the sake of future RER, maximising the exploitation of the tools within the European Union that may improve capacity as far as diagnostics and the treatment of numerous pathologies, namely, rare diseases are concerned.

Highly specialised centres are commonly referred to as “Centres of Excellency” or “Reference Centres”. In fact, both terms are used indistinctly throughout Europe, a custom that has been made valid by the document discussed at the conference organised by the Spanish Presidency in Minorca, on the 31st of May and 1st of June of 2002, stating that the concept of "Reference Centre" is a synonym of "Centre of Excellence". However, it’ is considered as correct to, in Portugal, adopt the official designation of CR, considering that these centres may come to be part of the RER and not the European networks of excellence.

Through this process of identification, official recognition and diffusion of CR in Member States, based on the hierarchy founded on knowledge rather than only on a geographic level, it is expected for the highly specialised healthcare offer will be equivalent to significant improvement in quality, effectiveness and safety. On the other hand, the potential of medical science and health technologies will also grow with the vital and inherent sharing of knowledge and training of health professionals in Europe. The desired outcome, once finished the identification, approval and recognition processes for the CR, and once these are integrated with the RER, would then be to create a concept of synergy in the cooperation throughout Europe in the highly specialised healthcare fields, promoting economies of scale, maximising efficiency and ensuring the cost-effectiveness of healthcare practices, stimulating innovation and cultivating good practices.

That being so, and taking into account the binding transposition of the Directive onto Portuguese law, it is important to establish a course of action for the creation and the effecting of the CR in the Portuguese health sector, strengthened by the strategic positioning of the Portuguese health system on a European

scale, which has been acknowledged in **Major Planning Options for 2012-2015**, in regards to the strengthening of the cooperation in the field of health with the European Union.

Also worth mentioning that the **Programme of the 19th Constitutional Government** has presented as its main intentions: (i) to ensure the financial sustainability of the National Health Service (SNS), relying on the implementation of measures to rationalise costs and a more rational and efficient use of the resources available in the health sector, (ii) to reorganise the hospital network though a more cohesive and rational vision of the system, allowing for a concentration of resources, and (iii) to improve the administration of healthcare practices, so that the results will be in line with the best in Europe.

As such, and following up the Memorandum of Understanding performed with the European Union, the European Central Bank and the International Monetary Fund, the **Technical Group for Hospital Reform** (GTRH) was created with Order of the Minister of Health No. 10601/2011, of 16 of August, issued on the Official Journal, series II, No. 162, of the 24th of August. In November 2011, the GTRH submitted their Final Report titled "The Citizens at the Centre of the System, The Professionals of the Centre of Change", where they defined eight Strategic Initiatives, each of them inclusive of a number of measures, the implementation and supervision of which will promote the commitment towards a plan of change with the length, depth and density required by a true structural reform of the Portuguese hospital sector. In the first Strategic Axes "A More Coherent Hospital Network", the GTRH proposed the identification, recognition and implementation of CR with the intent of presenting them as potential healthcare units for citizens of European countries and countries that are part of the Community of Portuguese-speaking Countries. Likewise, with the commitment to respond to the population's demand, the creation of CR will translate into the concentration of casuistry and resources for the diagnosis and treatment of different, less frequent medical and surgical pathologies, involving multidisciplinary teams and a more demanding control, with stronger focus on research and education.

Lastly, the National Health Plan (PNS) for 2012-2016 expects a process of adaptation of healthcare practices, from self-care to quality standards of healthcare services provided by the different organisations of the SNS. Although, the same PNS 2012-2016 holds a group of guiding rules in its strategic axes related to the Equality and Access to these services as well as the Quality this report answers to. And so, in the strategic axis related to the equality and access, it is proposed that the links

between the health service units be strengthened, clarifying the coverage and technical and service responsibility of each, as well as evaluating the suitability and efficiency of their response as a network.

Taking this into account, and also the non-existent official recognition of CR in Portuguese territory and the strategic importance of the constitution of such units in the health sector, a Work Team (GT) has been put together, pursuant to the **Order of the Deputy Secretary of State of the Ministry of Health No. 4319/2013**, of 15 of March, issued on the Official Journal, series II, No. 59, of 25 of March, to put forward a definition for CR, establish the criteria for the Ministry of Health to identify and characterise CR, propose a model for implementation and financing, as well as to plan out how such a concept would become a part of the Portuguese Hospital Network and the European Reference Network.

In general terms, all European health systems face the challenge of improving efficiency and reducing costs, while ensuring a better quality in the administration of services and the results achieved, in such a way that their growth and success will be guaranteed. However, healthcare does not stand for a simple, standardised activity; it requires responses to demands of different natures resulting from diverse clinical situations, sometimes complex and, more often than not, fragmented and of difficult access. Healthcare practices are usually undertaken by numerous professionals who act on different levels across the health system, without proper coordination or a holistic perspective. It is of importance, then, to invest in the creation of structures that will provide healthcare services, strongly promoting cost/effectiveness relations while administering those services and guided by a mission centred on the permanent improvement of outcomes.

Considering how scarce and how much of a burden human resources and materials can be, maintenance or quality improvement in a health system must abide by a concentration logic, in order to ensure: (i) efficiency and effectiveness; (ii) appropriate performance in terms of structures, procedures and results; (iii) safety for both patients and professionals; and (iv) satisfying the expectations of patients and professionals.

In fact, a strong scale/quality ratio is visible in the majority of health systems, making it so that service units of a bigger scale tend to invest more on communication between specialties, reinforcing multidisciplinary work, ensuring an optimised use of diverse technology and creating a propitious

environment for permanent education and research. As such, and considering these synergies, healthcare practices that benefit from economies of scale must be concentrated on this task.

This course of fragmentation of healthcare often implies worse results in terms of quality of healthcare administration and waste in terms of efficiency. Effectively, one can see that citizens often get lost in the system, and don't reach services in due time (or do so with considerable delay or duplications). Therefore, opportunities to obtain considerable profit when promoting healthcare practices focused on the patients' interests, and so guaranteeing the coordination of health services and the practices carried out efficiently and safely, must not be neglected. Despite the unity of each organisation, the “habits" of high quality healthcare practitioners are characterised by the detailed planning centred on the patients’ needs; by the commitment towards the results; and by the commitment of the team towards the continuous improvement of quality. Clinical quality and safety then require a multidisciplinary coordination, pointed towards the disease and the patient and focused on the satisfaction of the citizens’ healthcare needs. The design of this healthcare network must then dynamically combine safety, economies of scale, availability and quality of services, as well as accessibility. Strictly speaking, this design must be supported by an information system adapted for these goals, and also a monitoring and assessment system of the results reached.

Keeping this in mind, it is important to promote the transition onto the management of subpopulations of patients with similar clinical conditions, implementing better practices based on scientific evidence, sharing and promoting such good practices, identifying and acting when opportunities for improvement arise, promoting clinical research, achieving economies of scale and using resources as efficiently as possible.

If the Portuguese health system doesn’t follow this path, instead straying away from the opportunity to recognise national CR which, on the one hand, offer economies of scale on a national level and, on the other hand, may come to be part of future RER, it will be isolating itself from the exchange of knowledge, sustainability, reputation and challenge the remaining European health systems will be benefitting from, limiting itself to exporting complex clinical conditions instead of presenting itself as a focal point in specific fields and complex conditions occurring in other countries across European land.

The creation of CR will give services credibility as the focal point of other continents, namely of the countries of the CPLP.

The establishment of CR presents itself as imperative also in terms of developing skills and discerning of the different national hospital layers. In fact, Portugal's geographic and demographic dimension makes it so that the concentration of certain pathologies in selected locations forms an essential condition for the safety of patients and the achieving of better results. The intersection of the CR network with the RRH is, consequently, vital, as it is foreseen that their evolution throughout the next few years will become a factor for scientific and technological differentiation, as well as responsible for the progressive improvement of health indicators, be it in terms of outputs or outcomes. Also worth to mention is the distance various European countries have already covered, for instance Denmark, which has proceeded to the concentration of the treatment of certain pathologies into a unique centre and, in some cases, arranged for the forwarding of patients with certain pathologies to other countries, in cases where such a procedure proves itself more cost-effective.

2 GOALS

Facing the need to establish a plan of action for the identification, recognition and materialisation of CR that will respond to the needs of the country and, simultaneously, have the potential to eventually be part of the future RER and, abiding to the measures recommended in the Final Report of the GTRH and the implications present in the Directive, the aims of this Work Group and this report are:

i) To define the concept of CR;
ii) To define national criteria to support the identification and recognition of CR;
iii) To put forward a plan of implementation for the CR;
iv) To propose the general criteria for the functioning of the CR;
v) To define a model for the CR to become part of the national RRH;
vi) To propose the general lines of the functional and organising model that is to support the creation process of the CR;
vii) To frame and apply national politics on the matters of rare diseases, as well as a group of already existent measure and references to organising models which have been in the origin of the CR now proposed in light of the creation of CR;
viii) To present priority areas, pathologies and procedures that may come to shape up the first CR in Portugal.

3 METHODOLOGY

The underlying methodology of this report is supported by the following main pillars:

i) Aims and notions present in Directive 2011/24/EU, of 9 of March;
ii) Programme of the 19th Constitutional Government;
iii) Goals presented in Major Planning Options for 2012-2015;
iv) Conclusions of the Work Group's Final Report;
v) National Health Plan 2012-2016;
vi) The need for the development of CR and their inclusion in the Portuguese hospital network and in the RER.

The Work Group then proceeded to reviewing the official European literature on this matter, as well as applying the information learnt to the task at hand, in which Portugal has had a role, as part of the European Cross-border Healthcare Committee and the Experts' Group for the RER of the European Commission.

In a first stage, the Work Group approached the state-of-the-art of the development of the CR across the Member States of the European Union, in order to insert the Portuguese reality in context in terms of legislative and normative framework and current models in administration of more distinguished and specialised healthcare, discussing the existence of statutes given to institutions or services, as is the case with that of High Differentiation Centre (CED), Treatment Centre (CT) and Centre of Excellence.

On top of the describing the European and national contexts, this report found its foundations in national reports on reunions of the European Cross-border Healthcare Committee and the Experts' Group for the RER on the matter of Cross-border Healthcare.

The Work Group resorted to literature published on *Web of Knowledge* and *Google Scholar*, in order to identify the first priority areas of intervention for the development of CR in Portugal, so as to respond to the need of concentration of resources such as quality standards of healthcare practices, which is in turn linked to the rising of efficiency levels, as well as the need to identify CR in Portugal with the prospect of having them eventually become part of the RER.

The data used belongs to official national and international sources, properly identified.

The bibliography consulted on the subject of this report is presented as its own chapter.

The Work Group has also consulted with Directorate-General for Health (DGS) and the Portuguese Institute of Blood and Transplants, I.P..

4 HISTORICAL BACKGROUND

The report "The Health Sector: From Rationalisation to Excellence", presented by Porto Business School for Health Cluster Portugal, states that Portugal will hardly hold a competitive sector without creating an internal market that will confront corporations and institutions with the same level of demand they face from outside and motivating an international perception that the Portuguese health sector presents competitive cost-effectiveness patterns on par with other countries. This report adds that Portugal's reduced territorial dimension and the growing external competition would recommend the concentration of resources, both human and financial, in fields of knowledge and production, contributing to the success of the success of the health sector internationalisation strategy.

As previously mentioned, the Major Planning Options for 2012-2015 recommend the strengthening of the cooperation in the health field in the European Union, in order to create conditions for the application of the Directive on the application of patients' rights in cross-border healthcare.

The Directive states that the European Commission must support the development of RER and CR in the Member States. On the other hand, it is in charge of the European Commission to adopt a list of criteria the networks must comply with, as well as the conditions and criteria the national CR that wish to join the RER must fulfil.

Thus, the concepts of CR and RER became one of the relevant topics approached during political, legal and strategy debate on the "movement of patients" by the European institutions and Member States.

In such context, in 2009, the European Commission created a Committee of Experts on Rare Diseases, named EUCERD, where the Portuguese Ministry of Health is officially represented. This Committee elaborated, approved and proposed to the European Commission two important documents:

i) The Recommendation on Rare Diseases CR Quality Criteria, in October 2011, defining the task and goals of the CR for rare diseases, as well as the process and criteria for its classification and assessment;
ii) The Recommendation for Rare Diseases RER, in January 2013, defining the task, goals and activities of the RER for rare diseases.

The European Commission also established, in 2012, a Committee on Cross-border Healthcare and an RER Expert Group for Cross-border Healthcare, with the Portuguese Ministry of Health officially represented in both and participating, from the very beginning, in consultation and counselling for the European Union. While that Committee accompanies the implementation of the different aspects of the Directive, the Expert Group has the task of advising the European Commission on the specific list of criteria and conditions the RER and CR wishing to join must obey to, and it is expected for the official Decision of the Commission on this matter will be issued in the first trimester of 2014 and that, in the first trimester of 2015, the Commission will proceed to starting the application process for the creation of RER, so that the first European networks will be operating by the last trimester of that year.

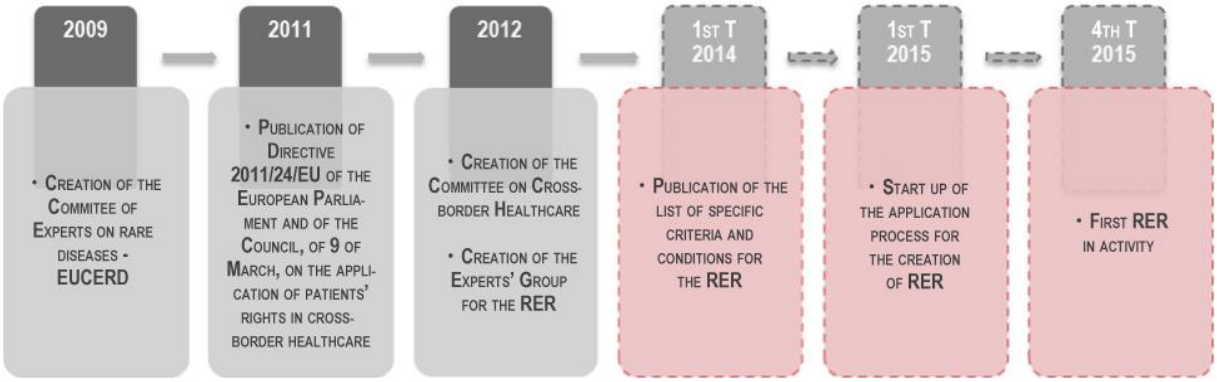

Image 1. Main stages along the process of creating RER.

It will come down to the European Commission to outline the management model for RER, which may come to have different architectures and internal relations, as well as its structural elements, in order to be led through suitable technical and coordinating structures, transports, effective and efficient.

However and regardless this process on a European scale, it is beneficial, for reasons previously presented, for the country to be fit with CR in specific fields within the area of healthcare. With that in mind, and in regards to the autonomy in the management of its health system, it is Portugal's responsibility to define its own criteria for the identification and official recognition of national CR, regardless of whether or not these become a part of the RER. For these CR to be acknowledged as such on an European scale and join the future RER, the criteria to be submitted must then be in line with the criteria and conditions being officially defined by the Commission on a European level.

Because of this, Portugal must review and adapt to the context of the Directive the decisions and recommendations of the European Union what had until then been defined on the matter of high specialisation and rare diseases within the national health system. On this note, one must emphasise the need to review the following concepts of healthcare specialisation:

i) The figure and prerequisites of “High Differentiation Centre” and “Treatment Centre", created through DGS Regulatory Circular Letter No. 14, of 31 of July, with the aim of assuring patients with chronic pathologies, which require specialised resources, the access and specific financing to highly differentiated healthcare, for which a special concentration of infrastructures and skills were necessary. Some examples of fields for which CED and CT have been established would be multiple sclerosis, obesity, vascular access for haemodialysis, nephrology and type 1 diabetes through continuous subcutaneous insulin infusion;
ii) The National Programme for Rare Diseases, approved by the Minister of Health on the 12th of November of 2008, which, in this current context, must evolve into a national strategy for an cross-sectoral approach of rare diseases, actively involving the clinical, genetic and pharmacological research sector and the patients’ associations;
iii) The National Reference Centre Network for Rare Diseases, approved by the Minister of Health on the 17th of January of 2011, which, in this current context, must be adapted to the CR that may come to be officially recognised in this area by the Ministry of Health;
iv) “Comprehensive Haemophilia Treatment Centre” institutions, created by Order No. 8811/2011 of 25 of May, of the State Deputy Secretary of Health, which must be revised in the light of the concept of CR;
v) “Centre of Excellence” institutions, created by Order No. 2545/2013, of 7 of February, of the State Secretary of Health, for diagnostic and treatment of lysosomal diseases which, in this context, must be reviewed in light of the concept of CR as was proposed by work currently being carried out on a European scale.

Currently, the CED and CT available in Portugal are as presented in Attachment 1 of this document.

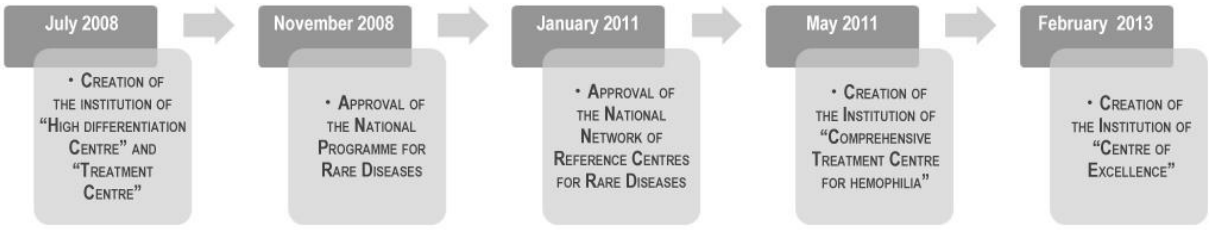

Image 2. Main stages along the process of establishing institutions as CR and the National Programme for Rare Diseases.

It is important, then, to proceed onto the future insertion of these structures in the new model now predicted in order to unify and clarify criteria.

4.1 EUROPEAN STATE-OF-THE-ART ON REFERENCE CENTRES

Currently, most Member States make progress in the process of internal development of identification and recognition of CR at different speeds.

The European Observatory on Health Systems recently published a general vision of the current status on a European level, which reaches out to the majority of the countries highlighted on the map below and is then summarised:

Source: http://europa.eu/about-eu/countries/index_pt.htm

Image 3. Map of Europe.

GERMANY

In the 16 federal states of Germany, the diseases diagnosed and treated in highly specialised centres are oncological diseases, pulmonary hypertension, haemophilia, tuberculosis, multiple sclerosis, acute cardiac insufficiency, AIDS, rheumatism, Wilson disease and Marfan syndrome.

In this country, for a hospital to apply for specialised CT in one of these diseases, it must satisfy various criteria reviewed every two years. On top of that, there are other tools to ensure the quality of highly specialised healthcare practices, namely, through the certification and accreditation of services.

Germany has also been developing competency research centre networks since 1990, now possessing 17 networks on depression, schizophrenia, Parkinson disease, cerebrovascular accident, leukaemia, malignant lymphoma, paediatric haematology, rheumatic diseases, hepatitis, HIV and congenital cardiopathy.

BELGIUM

Clinical care requiring a special concentration of equipment, knowledge and skill in Belgium has been carried out at university or large-scale hospitals.

The concept of CR is currently associated to the treatment of rare and chronic diseases. These centres are picked by means of spontaneous applications, based on criteria established and adopted by specialists. This criteria include multidisciplinary approaches, the clinical team members' skill, the number of patients treated and supervised, and also geographical distribution and networking with local practitioners. There is, however, no national criteria standardised to select the type of pathologies assigned to these centres.

Besides the eight centres specialised in human genetics, there are six multidisciplinary centres specialised in neuromuscular diseases, four in refractory epilepsy, seven in cystic fibrosis and eight in rare monogenic inherited metabolic disease. Other centres possess high competence and expertise for

the treatment of AIDS, chronic respiratory disease, chronic fatigue syndrome, chronic pain, autism, cerebral palsy and spina bifida.

DENMARK

In Denmark, a national council has the authority to define the prerequisites and approve the criteria applicable to what they call specialised functions or competencies for the diagnosis and treatment of diseases and conditions that require services of considerable complexity and the presence of numerous multidisciplinary partners. Generally, this country invests most of its expertise, experience and/or resources on rare diseases, and the main criteria are the complexity and rarity of the pathologies.

A specialised competence is only assigned to a department of a public or private hospital that has been officially recognised for that end, meaning it has been considered a regional or national CR. These specialised competencies were grouped, according to their complexity, rarity and required resources into: **regional** (when they present a mild level of complexity, are relatively uncommon and require a considerable amount of resources, such as the collaboration with other specialties) and **national** (when they present a high level of complexity, are very rare and require a large number of resources and the collaboration with a significant number of specialties).

Denmark refers patients in need of intestinal transplants, those that require particle radiotherapy, foetal surgeries and intracranial bypasses for treatment abroad.

SLOVENIA

Among the three levels of healthcare services in Slovenia, the tertiary level, which encompasses university institutes and hospitals, provides high differentiation healthcare services in professional, technological and educational terms all across the country. The statute of “Tertiary Centre” is awarded by the Ministry of Health, based on success on satisfying multiple criteria of educational, scientific, professional and research natures, which, in a way, leads to the classification of those services as

analogue to national CR, qualified to provide more demanding specialised healthcare. The concept of CR, as a service unit providing healthcare is not yet defined by law. In blunt terms, CR are all of those that comprise entities complex clinical cases are referred to, collaborate with other institutions and have gained international recognition, namely, through research and scientific publications. The Slovenian Ministry of Health, in the meantime, has created a FT for the definition of CR for rare diseases.

SPAIN

In Spain, Law No. 16/2003, of 28 of May, establishes the legal basis for the constitution of CR in areas to define. The legislation establishes the legal framework for coordination and cooperation between the public health authorities and the CR which demand the centralisation of cases into a small number of centres to ensure a better management, the access quality and the quality of specialised healthcare, safe and efficient. The effective creation of CR in Spain is regulated by the Royal Decree No. 1302/2006, of 10 of November, which lays out the procedure basis for the appointment and accreditation of CR for the diagnosis and treatment of a rare pathology or a group of rare pathologies and the development of specific techniques. The methodology to recognise these centres is based on the identification of needs, estimates on costs for each disease and the annual publication of recognised CR per pathology. There is a Committee in the Inter-territorial Council of the National Health System that studies demand and proposes eligible diseases as well as technical conditions for the creation of a CR, defining a suitable number of centres and their strategic localisation. A demonstration of skill, casuistic methods and expertise when approaching a disease, human resources, technicians and technological infrastructures associated to the procedure in hand and the existence of a quality and patient safety system represent criteria for the official recognition of these centres. Currently, there are 177 CR[1], dealing with fields such as severe burns, auricle reconstruction, congenital and infantile glaucoma, congenital eye disturbances, paediatric and adult ocular and intraocular tumours, orbital decompression in thyroid ophthalmopathy, orbital tumours, retinopathy of prematurity, ocular surface complex reconstruction, total body electron irradiation for mycosis fungoides, treatment of germ cell tumours with intensive chemotherapy, paediatric liver and kidney transplant, liver transplant on adults, paediatric and adult lung transplant, adult heart-lung transplant, paediatric heart transplant, pancreas transplant, paediatric and adult intestine transplant, kidney transplant, transsexuality, pelvic osteotomy

for hip dysplasia in adults, treatment of resistant osteoarticular infections, orthopaedic treatment for neuromuscular diseases, myelomeningocele, congenital short femur, tibial agenesis, osteogenesis imperfecta, limb lengthening, microsurgery reimplants, musculoskeletal tumours, hematopoietic stem cells transplantation for chronic myeloid leukaemia in children, congenital heart disease in the new-born and complex congenital cardiopathy in children, congenital heart disease in adults, mitral valve complex reconstruction surgery, paediatric arrhythmology and electrophyisiology, hypertrophic cardiomyopathy, brachial plexus surgery, refractory epilepsy, movement disturbances, brain neuromodulation of refractory neuropathic pain, hereditary ataxia and multiple sclerosis.

BALTIC STATES: ESTONIA, LATVIA AND LITHUANIA

In the Baltic States, the concept of CR has not yet been adopted. Due to the fact that populations of these countries are too small in numbers to sustain services of high expertise and also the circulation of patients, the Baltic States are considering the idea of sharing resources between themselves.

In Estonia, one of the most recent advances on this matter is the layout of a national strategy for the quality of oncological healthcare, establishing, on a national level, the prerequisites of the CR for cancer treatment.

Latvia has a special finance programme for highly specialised treatments of specific diseases; such is the case with coronary angioplasty and multidrug-resistant tuberculosis, which are only available at a very restricted number of centres.

In Lithuania, high competence healthcare is practised mostly in two university hospitals and one national centre of oncology. These institutions follow a multidisciplinary approach, with a vast spectrum of diagnostics technology, follow-up, treatment, teaching, training, research and international collaboration in the fields of clinical practice and research. Recently, a reference pilot-centre for cystic fibrosis has been created, following about 50 patients per year.

FINLAND

In this country, the highly specialised service spectrum is carried out by its five university hospitals. To this date, this university hospital network has been known as the informal Finnish model of CR. The main areas these centres work on include: rare paediatric diseases, transplants, severe burns, complex surgical treatment and spine trauma.

However, the procedure to officially define the type of healthcare to be practiced by the CR has not yet been standardised, while it is expected for government action on the formal creation of CR to take place, namely in the fields pertaining to cancer and rare diseases.

FRANCE

Since 2009, the creation of 17 national centres for the treatments of rare cancers has been green-lit. The acknowledgement of CR for rare diseases was announced in 2004, putting together centres that excel in their fields of competence, comply with clinical protocols, carry out epidemiological studies, develop teaching activities and contribute to research on an international scale. These CR keep a tight link with the regional structures most within the patient's reach. Currently, there are 131 regional CR for rare diseases, which are connected with 500 regional centres, less differentiated. Each CR for rare diseases may encompass various units, in places fairly separated geographically, as long as they form a coherent entity to support one or a group of rare diseases. The recognition process for the CR for rare diseases demands the submission of an application by the interested healthcare units, approved by a national committee that also lays down the criteria for the geographical distribution of centres based on epidemiological data. The recognition of CR for rare diseases is officialised, for a period of five years, by order of the Ministry of Health. By the end of the third and fifth year of activity, the CR is subjected to a process to assess and revalidate its recognition, led by the High Authority of Health. The CR for rare diseases currently in activity work on the treatment of autoimmune and cardiovascular diseases, growth anomalies and malformation syndromes, dermatological, hepatic and haematological diseases, hereditary metabolic disorders, neuromuscular, ophthalmological, lung, kidney and hereditary diseases and rare malformations of the head and neck.

GREECE

According to the Greek legislation that regulates the country's national health service, a specialised hospital may be classified as a specialised centre, so long as it is involved in the practice of specialised healthcare in a specific medical field, coordinates the services offered, takes action in the training and specialisation of its medical, nurse and other types of staff, and develops research measures. This legislation also establishes the procedures to be taken in order for specialised centres to be recognised and managed. The same principles apply to clinical units and laboratories belonging to universities or other public organisms, which may be recognised as specialised centres. Through this process, and within the referred legislation, numerous specialised centres have been recognised, namely, for the treatment and supervision of patients in the fields of tuberculosis, primary immunodeficiency, brain anomalies in children and haemorrhagic disease in children. There are also centres specialised for diseases of the occupational kind. Additionally, many clinics and laboratories offer specialised services in the field of rare diseases, in practice acting as a CR.

An example of the Greek organisation is the Paediatric Health Institute of Athens, considered a CR for new-born screening, encompassing all new-borns in the country and covering congenital metabolic diseases, genetic syndromes and diseases and metabolic bone diseases. There are also two centres and three university clinics specialised in cystic fibrosis, besides the other centres specialised in other diseases, such as muscular dystropthy

There is currently an acknowledgement of the need to have official criteria established and procedures standardised, as well as the implementation of a general framing of administration of the CR.

NETHERLANDS

In Netherlands, a strategy for the concentration of the offer of healthcare in highly specialised units has been encouraged, with the intention of ensuring better quality of healthcare practices and safety for the

patients. At this point, the creation of CR is a priority in the government policy, as part of a plan to improve access to highly specialised healthcare and to promote research. A mandatory prerequisite of the CR in Netherlands is mutual cooperation, and the establishment of a CR for Parkinson's disease is currently in development.

HUNGARY

In this country, most of the CR are linked to university hospitals, working mostly on specific and rare diseases, which require expertise on a certain field and offer patients access to diagnosis, care and equipment as the need arises. Activity in these centres includes research, teaching and training. In 2008, a national centre for rare diseases functioning as a CR was created by order of the Ministry.

ITALY

In Italy, the concept of highly specialised centre on a national level appeared after 1990 on the subject of treating rare diseases and transplantations. In 2001, CR for rare diseases were established, recognised by regional health authorities. There is one national centre for rare diseases at the Institute of Health, responsible for supervising those CR and mapping the geographical distribution based on pathologies. Likewise, there is a National Centre of Transplantation that coordinates all activity pertaining to transplants on a national level.

MALTA

As a small country with a reduced population, Malta refers a large number of its patients in need of highly specialised healthcare abroad, especially to the United Kingdom, with which it has a specific partnership for this very end, and as such healthcare practices performed they are considered as an extension to Malta's own health system, to the point of boasting a state travel agency that unifies the procedures related to moving patients to the United Kingdom.

POLAND

In this country, there is a certain number of hospitals with a high level of competence and expertise, working on the most complex cases within a specific field, as is the case of the institutes of psychiatry and neurology, physiology and hearing pathology, maternal and child health, rheumatology, cardiology, tuberculosis and lung diseases and centres for oncology and heart diseases. 13 centres for trauma, specialised healthcare and multiple trauma patients were also recognised.

As such, hospitals that follow the additional prerequisites, meaning they possess the best equipment and most highly qualified staff, also offer services of high expertise in fields such as endovascular surgery, teleradiotherapy, haemodialysis, hyperbaric oxygenation, organ transplant and heart surgeries.

UNITED KINGDOM

In the United Kingdom there is a national health service commission for specialised and highly specialised healthcare created roughly 25 years ago, which ensures the pinpointing of the demand, planning and recognition of the CR. There are about 60 service units that have been recognised as highly specialised centres. Units that intend to acquire the statute of CR must submit an application in order to prove the unit proposed can present better clinical results when compared to other alternatives currently available in the National Health Service. These CR take part in a national network that holds online meetings and discussions. The official recognition of each CR is renewed periodically by the government.

CZECH REPUBLIC

In this country, there are centres with high expertise for the Gaucher disease, cystic fibrosis, Fabry disease, pulmonary hypertension, hereditary ataxia, rare tumours and skin diseases. Recent legislation, from 2012, laid out the conditions for the creation of centres of highly specialised healthcare, in order to have those join/be part of the RER, and it is expected for the treatment of patients with rare diseases to be concentrated into 10 to 20 specialised countries, under the guidance of a national coordination centre. Since 2006, the Ministry of Health and the Czech Society of Oncology certified 18 centres, where they transferred the most complex and costly cases in the fields of diagnostics and cancer treatment. After an audit carried by the Ministry of Health, aiming to assess the quality of healthcare practices at the numerous centres, some non-compliances were taken note of, resulting in the reduction of certified centres to 13. For it to be certified, a centre must comply with a number of criteria, for instance in terms of human resources (number of specialised doctors, nurses, radiology technicians and biomedical engineers) technical equipment and methods of diagnostics, interdisciplinary cooperation, education, training, research and clinical trials. There is also a public centre on the national coordination of transplantations.

ROMANIA

In this country, hospitals are classified in five categories, depending on the level of knowledge and expertise, quality of medical equipment, human resources and the complexity of healthcare practices, and the top category is occupied by hospitals that present a high level of competencies. These hospitals also act as teaching, training and research units. The main CR are located mostly at public university hospitals for the treatment of diabetes, cancer, rare diseases and administration of critical healthcare practices. The process of recognition for CR in Romania is established; centres are officially recognised by the Ministry of Health.

SWEDEN

The concept of CR in Sweden rose in 1990 and spread out all over the country, encompassing diagnostics and the treatment of rare diseases, as well as those that require highly specialised medical competence and the assignment of differentiated technology and deal with fields such as oral surgery, cochlear implants in children, heart, liver and lung transplants, ocular tumours, paediatric heart surgery, treatment of severe burns, glaucoma in children and intra-uterine treatment, while the addition of advanced paediatric surgery is currently being considered. CR are officially approved by the National Council for Health, through a special commission of experts, created for this end.

Currently, Sweden is developing a partnership with Denmark on cross-border cooperation, and it has started by creating joint centres, namely for treatment of breast cancer and melanoma, aiming to make available the treatment for patients that demand a high level of specialisation and grow to become the European CR in Northern Europe.

The most relevant common aspects pertaining to the development of CR in some Member States for which there is information available are summarised in the table below.

Table 1. Most relevant common aspects between Member States.

COMMON ASPECTS BETWEEN MEMBER STATES							
Member State	Reference Centres officially recognised by the Member State	Reference Centres for Rare Diseases	Reference centres for specific diseases				
			Lung diseases	Oncological diseases	Transplantations	Oncological diseases	Cardiovascular diseases
Germany	x		x	x		x	x
Belgium	x[2]		x			x	
Denmark	x						
Slovenia		x		x	x		
Spain	x		x	x	x	x	x
Estonia				x			
Finland		x			x		
France	x	x	x	x		x	x
Latvia							
Lithuania			x				
Greece	x						
Netherlands	x	x					
Hungary	x	x					
Italy	x	x			x		
Malta							
Poland	x		x	x	x	x	x
United Kingdom	x	x		x	x		x
Czech Republic	x		x	x			
Romania	x	x		x	x		
Sweden	x	x		x	x		x

Source: Adapted from the European Observatory on Health Systems and Policies (2013).

[2] While there is legislation on the matter, there are yet no CR recognised in accordance with these laws. "*More formally, the concept of reference networks is mentioned in Article 14 of the Federal Hospital Act. It provides for the specification of characteristics for designating reference centres. Even though the Minister in 2005 indicated the intention to implement this article, it has not been done so far*" (European Observatory on Health Systems and Policies, 2013, p. 19).

For centres to be categorised in this document as officially recognised, the Work Group has considered countries where there is national legislation on the matter and the centres approved in accordance with said legislation. All other are specialised centres, although they are not formally recognised as national CR.

5 REFERENCE CENTRE IN PORTUGAL

Similarly to what has been occurring in most European countries, what matters now is for transpose a group of definitions that establish the foundation for the constitution and the model for implementation and develop national CR to the national context on various levels (especially organisational, functional and financial levels).

Reference Centres are units that provide healthcare with certified technical knowledge in the administration of healthcare practices of high quality to patients with certain clinical conditions that require a special concentration of resources or skill due to the reduced frequency of the disease, the complexity of the diagnosis or treatment and the high costs of those same conditions. They must:

i) Integrate multidisciplinary teams in their constitutions, strongly qualified in their field of practice, as well as highly specialised structures and medical equipment, which must be concentrated;
ii) Ensure healthcare practices and services are administered in accordance with the highest quality standards, in conformity with the clinical evidence available and the specific recommendations of the scientific community;
iii) Possess competencies in the fields of teaching/training and research to be regarded as a medium for innovation.

The core of CR may have its basis on the global approach of one specific disease alone or a group of diseases, and they may focus on one procedure alone or a group of them.

Taking this into account, the main structural characteristic of a CR must be:

i) Differentiation;
ii) Appeal;
iii) Consultancy ability and availability;
iv) Innovation;
v) Teaching;
vi) Research.

CR must also focus their practices on a group of action principles that support their activity in its entirety:

i) Quality improvement;
ii) Access improvement;
iii) Effectiveness improvement;
iv) Focus on outcomes;
v) Safety improvement and minimising clinical risk;
vi) Transparency.

National CR may come to act as RER elements or links.

In fact, considering the CR recognition process on a national level of each Member State carried out by the respective competent authority, in Portugal, it will come down to the Ministry of Health to recognise the Portuguese CR which, afterwards, may voluntarily choose to submit an application to the European Commission to join a RER. Such CR must, during the assessment evaluation on a European scale, show that they abide by criteria to be defined by the Commission and point out the one in charge of the CR, which is formally communicated to the European Commission by the national competent authority.

Each CR that may come to join a RER as a member must have a defined representative, whose task will be to represent the role of a CR inside the RER it has joined, link the RER and CR together, take part in the governing council of the RER and collaborate with and advise the coordinator of the RER on all kinds of questions related to its field of specialisation.

However, in each Member State there may be CR that, although they are officially recognised on a national scale as CR in that Member State, they are still not recognised by the European Commission as CR to join a RER.

In such cases, each Member State may decide to propose to the Commission a tight collaboration between some of those national CR and the RER, so that they may benefit of the practices and work equipment in those RER in specific highly specialised healthcare fields.

The Member States are in charge of the decision to identify, analyse, evaluate and recognise national CR, and this information must be officially communicated to the European Commission by the competent national authority.

National CR that do not officially join a RER may, however, collaborate with them and become instead a **National Associate Centre** (CNA), so long as they possess the knowledge and expertise on the specific field of a RER and are recognised as national CR.

A CNA must provide highly specialised, safe and high quality healthcare practices, showing relevant knowledge and skill in a specific field of health for that same end. This field of competence and expertise must encompass specific diseases or other clinical conditions, also acted up by a RER.

The terms for the collaboration of each CNA with a RER entail its prior official identification and recognition by the Member State of origin and the ambition of said Member State and its CNA to collaborate with the RER in order to give assistance in reaching their goals, using relevant and suitable tools, namely information systems, clinical recommendations, protocols, reference criteria, training and research.

On the other hand, in our country there can also be centres that do not follow all the conditions and criteria for them to be officially recognised as national CR. In this case, if they possess knowledge and expertise in a certain specific field of competence acknowledge by the Portuguese Ministry of Health, through explicit and transparent procedures, they may be officially recognised as **Affiliate Centres** (CA) on a national scale; these will have to form a link with the national CR of the same specific field of competence to work on a network basis.

The CA must be identified and recognised by the Portuguese Ministry of Health, which must include the criteria used and the identification of the field or branch of specific competence of each centre, in order to form a web and integrate the RRH, taking into account its field of specialisation or differentiation.

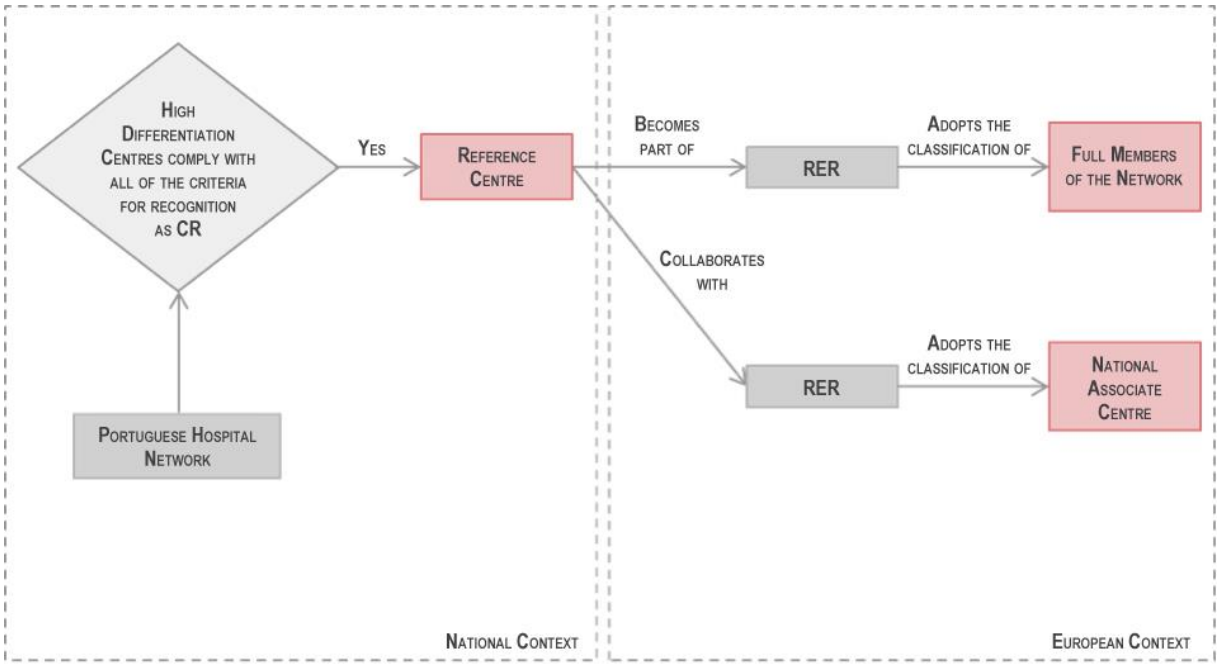

Image 4. CA and CR partnership model within the Portuguese hospital network and the RER.

6 LEGISLATIVE AND NORMATIVE FRAMEWORK

The regulation of future CR in Portuguese territory, as well as their partnerships with future RER, must abide by Directive 2011/24/EU and the general and specific criteria to be approved by the European Commission. The constant development of the RRH makes it imperative to incorporate the CR in the Portuguese hospital network, considering the presuppositions and criteria defined for the constitution of these highly specialised clinical centres, becoming an exemplar of competence, knowledge and technical and technological highly differentiated resources.

So, in order to officially identify, constitute and recognise CR in Portugal, one must keep in mind both the current European and national legislation, as Directive 2011/24/EU is one of the pillars for the development and recognition of the CR, and it is the Member States' responsibility to ensure the CR comply with the legislation with the country of origin. Due to existence of regulations rectifying statutes like those of CED, CT and CE, there will be a need to subject these to some adapting, in order to make it possible for these centres to satisfy the criteria for their recognition as CR, CNA or CA.

6.1 DIRECTIVE 2011/24/EU, OF 9 OF MARCH, OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL ON THE APPLICATION OF PATIENTS' RIGHTS IN CROSS-BORDER HEALTHCARE

Article No. 114 of the Treaty on the Functioning of the European Union lays out the main legislative foundation of Directive 2011/24/EU, which establishes rules to ease the access to safe cross-border high quality healthcare and promotes the cooperation on healthcare-related procedures between the Member States, in full respect of the national competencies in regards to organisation and administration of healthcare practices. In line with the vast jurisprudence of the Court of Justice of the European Union that raises questions pertaining to cross-border healthcare, with particular attention on the reimbursement of costs related to those healthcare practices, confirming that not even their distinctive nature or the way they're organised or financed may lift healthcare from the basic principle of free access, the present Directive aims to ensure a more general and efficient application of the principles established by the Court of Justice in a per-case basis, establishing rules to ease access to cross-border, high quality healthcare in the European Union and promoting the cooperation between

Member States as far as healthcare is concerned and simultaneously respecting the responsibilities of the Member States in regards to the internal definition for practices and management within healthcare.

The Directive ensures the reimbursement of costs sustained by a patient being provided with cross-border healthcare, if these particular practices are listed in those the patient would have had the right to benefit from in the affiliate Member State, thus ensuring the mobility of patients within Europe.
As such, the Directive figures **affiliate Member** as the competent State to provide prior authorisation for access to suitable treatment outside the State of residency according to Regulations CE No. 859/2003, of 14 of May, No. 883/2004, of 29 of April, No. 987/2009, of 16 of September and No. 1231/2010, of 24 of November. If no Member State is competent in the terms referred in the regulations, the affiliate Member State is the one where the patient is held or has the right to sickness benefits in compliance with the law of that Member State. Member States are therefore accountable for the administration of safe, efficient and high quality healthcare practices. For patients who seek healthcare in another Member State, either the Directive or the community regulations mentioned above are applicable. If the respective conditions are met, the patient cannot be deprived of the application of the instrument that guarantees him/her more favourable rights.

Cross-border healthcare is practiced in accordance with the national law of the Member State offering the treatment, following the rules and instructions on quality and safety established by the Member State offering the treatment, as well as the legislation of the European Union concerning safety rules.

The national contact points of the **Member State offering the treatment**, meaning those where the patient effectively receives treatment, must provide information on the health professionals legally practising in their territory.

All kinds of healthcare practices are encompassed by the Directive, the one exception being continuous healthcare services designed to support people in need of assistance to carry out daily routines; the allocation and access to organs and transplantation purposes and, with the exception of chapter IV, the public vaccination programmes against infectious diseases aimed exclusively at protecting the health of the population of a Member State are subjected to due planning and specific application measures.

The Directive expects and supports the continuous development of RER between healthcare practitioners and specialised centres in the Member States.
For this end, the Commission:

i) Must adopt a list of criteria and conditions the RER must comply with, as well as the conditions and criteria required to the healthcare practitioners who wish to join those networks. These conditions and criteria seek to ensure that the RER:
    a) Have suitable skills and knowledge to diagnose, follow and manage patients at their disposal, based on the positive results achieved;
    b) Adopt a multidisciplinary approach;
    c) Possess a high level of knowledge and skills that allow them to elaborate instructions on good practices, apply measures based on results and ensure quality control;
    d) Contribute to the development of research:
    e) Organise education and training activities;
    f) Collaborate closely with other centres and networks of highly specialised knowledge on a national and international scale;
ii) Must elaborate and publish the criteria for the creation and assessment of RER;
iii) Must make the exchange of specialised information and knowledge easier for the creation of RER and their assessment.

The Directive must also promote the cooperation and exchange of scientific information between Member States on the matter of voluntary networks by the national authorities responsible for e-Health and the assessment of health technology.

6.2 HOSPITAL REFERENCE NETWORK

The RRH is a concept developed during the Operational Programme for Health - HEALTH XXI, following up the main recommendations of the Sub-programme for Health 1994-1999, which was established during that time as the reference board to support the health sector structural reform

process. On its priority concerning the improvement of access and high quality healthcare, measure 2.1 of the programme mentioned above (“Hospital Referral Network") contemplated the implementation of RRH by specialisation seen as priorities, for the sake of functional articulation between hospitals, depending on the differentiation and identification of a set of services, in order to respond to the population demand, guaranteeing its right to protection and access in healthcare. RRH set out to regulate and plan out the cooperative system between hospital institutions, contributing to the optimisation and efficient management of the use of resources. Although there is no specific legal support maintaining the RRH, some of those that were published earned ministerial approval.

The elaboration process for the RRH has turned into networks, which in turn render into an organisational and reference model of the patients throughout the SNS of medical specialisations, while there are others expressing organisational and reference models in the form of techniques and procedures (such is the case with the RRH for Cardiology Intervention). The next image illustrates the chronogram of the creation of RRH for hospital medical specialisations.

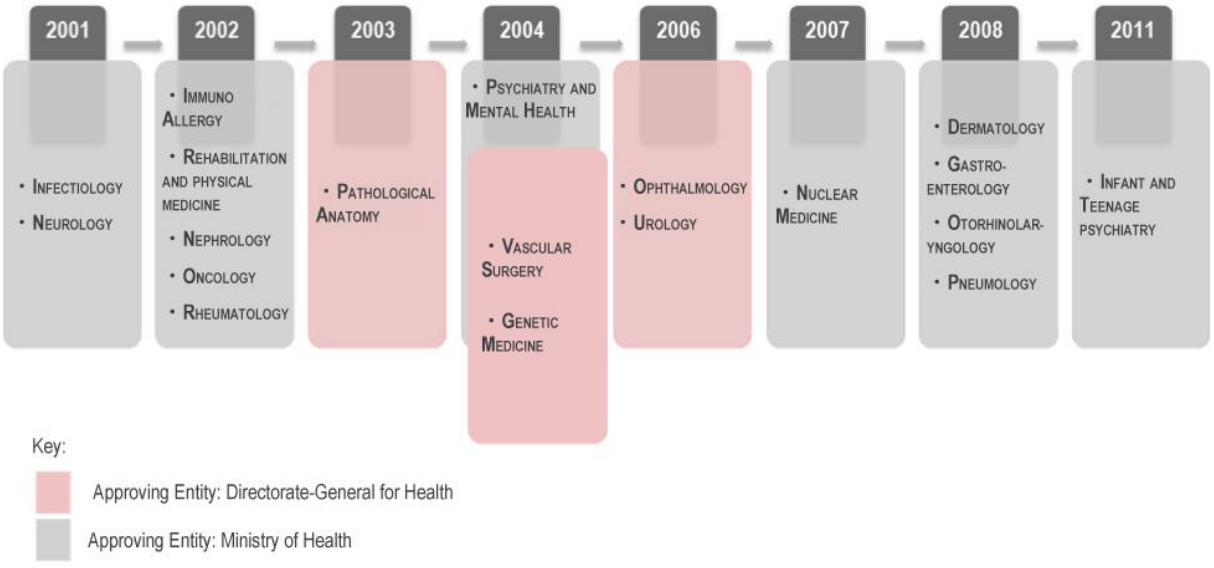

Image 5. Year of production and approval-entity of the published RRH.

Of the 47 medical specialisations defined by the Medical Association, 41 are specialised medical hospitals. Among those, 19 specialisations are practised at the RRH, and as such there are 22 medical

hospital specialisations that lack RRH. Of the 19 specialisations practised, 14 were designed over 5 years ago.

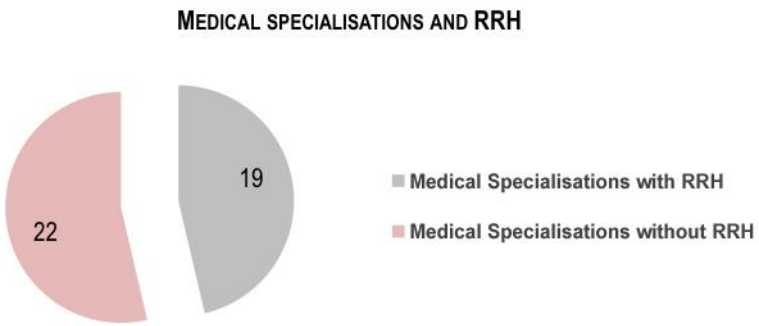

Image 6. Number of medical hospital specialisations practised at RRH.

6.3 OTHER NORMATIVES

Through Order No. 4325/2008, of 19 of February, DGS Circular Letter No. 14, of 31 of July of 2008, DGS Circular Letter No. 17, of 4 of August of 2008, DGS Circular Letter No. 18, of 11 of August of 2008, DGS Circular Letter No. 19, of 12 of August of 2008, DGS Guidance No. 13, of 9 of May of 2011, and DGS Guidance No. 32, of 26 of October of 2011, 16 CT were recognised for multiple sclerosis, 37 CT and 1 CED for obesity, 20 CT for vascular access for haemodialysis, 2 CED I nephrology and 15 CT for type 1 diabetes, through continuous insulin infusion, all of these included in Attachment one of this report.

7 IDENTIFICATION OF REFERENCE CENTRES AND AFFILIATE CENTRES

The identification and official recognition of each CR and CA on a national scale must be brought on by: (i) the need to concentrate or centralise highly specialised healthcare practices into a limited number of services and hospitals, without losing the criteria of proximity with the patient and (ii) the will to improve the clinical expertise and research in diagnostics and specific treatment.

As the national accountable authority, the Portuguese Ministry of Health is in charge of the decision to identify, analyse, evaluate and recognise national CR, and this information must be officially communicated to the European Commission. Of these national CR, some may, if they wish to do so, submit an application to join the RER, either as full members or cooperation partners as CNA.

The European Commission holds, by power of the Directive, the authority to define criteria, be it for the RER or the CR that may come to be part of the RER. Both the CR that comply with the criteria and conditions required by the Commission and become part of an RER and the RER themselves will be given permission by the Commission, under the rules it has defined, to use an official logo, as a specific European emblem, in order to be easily acknowledged without mistake.

Some of the criteria for the CR to become part of a RER will be valid for all CR, regardless of the practices of each RER, while some of it will be specific depending on the fields of practice of each RER.

On the matter of the national identification of CR, it is crucial to take into account the general and specific criteria defined by the European Commission and that way avoid, on the one hand, self-proclaimed CR and assist national CR that may come to submit an application to the Commission to become part of a RER.

As a general prerequisite, a CR officially recognised by the competent authority of its country may manifest its compromise to the European Commission to take part in, support and supervise the activities and work procedures carried out by RER which the CR intends on becoming a part of, in conformity with the conditions, criteria and procedures of that same RER.

The fact RER are not yet established does not stop the Member States from making advances in the process of identifying and officially recognising their nations' CR. On the contrary, all progress achieved on a national scale in this process will make the process of sorting through the fields of competence and specialisation the first RER will cover all the smoother.

In a European setting, the criteria the CR must comply with will depend on the pathologies specifically treated by the RER to be joined. Meaning that, on a European scale, a number of conditions and criteria of these natures will be defined: (i) horizontal and structural, which must be met for the centre to be recognised as a European CR, regardless of the treatments or medical procedures carried out, and/or (ii) variable, in accordance to the specific context of the RER. These conditions and criteria provide the Commission with the information input, quantitative and qualitative, from which the Commission with draw its own conclusions concerning the RER.

Currently, the European trend is for all countries to go forward with the national CR, thus gaining critical mass to eventually influence the creation of future RER. Portugal must, then, take on the same posture, which will then bring double gain. On the one hand, it's organised in order to guarantee better healthcare for the Portuguese, and on the other hand, the structure of the healthcare sector is adapted to the European challenges for the next few years.

The essential conditions and criteria the CR must comply with pertain to:

i) Clear mutual accountability for the patients;
ii) The administration of concentrated healthcare on the citizens;
iii) Efficient management and administration;
iv) Potential for research and training;
v) Exchange of skills and expertise;
vi) Information systems, preferably interoperable;
vii) e-Health tools;
viii) Good practices;
ix) Quality control;
x) Patient's safety;
xi) Assessment of the results.

Accordingly, for this effect of identification, the CR must satisfy, cumulatively, the **general criteria** presented in the tables below.

Table 2. General criteria pertaining to mutual accountability and healthcare centred on the patients.

General Criteria related to mutual accountability and patient-focused healthcare
To provide highly specialised healthcare practices, with high quality standards, safely and focusing on the patient
To safeguard the patients' privacy
To guarantee the patients their right to informed consent and information related to their state of health/condition
To ensure clear mutual accountability for the patients
To guarantee the entirity of the healthcare practices for the pathology/procedure being considered, approaching the process with an intergrated view
To guarantee access to the clinical expertise and technology needed

Table 3. General criteria pertaining to quality, safety and good practices.

General Criteria related to quality, safety and good practices
To guarantee a quality administrative system that will include a safety programme for the patients
To demonstrate process and result indicators
To guarantee a transparent mechanism of information on results, treatment options and quality and safety patterns in force at the Centre
To ensure capacity, knowledge and the skills to diagnose, supervise and manage patients with proof of good results
To actively measure the patients' experience and guarantee feedback reports
To possess the abilities for quality and safety benchmarking, as well as circulation of better practices on a national and international scale
Abide with the rules on personal data protection and accessibility to medical records and clinical information, in conformity with the national legislation and the provisions of the European Union on the matter

Table 4. General criteria pertaining to management and administration.

General Criteria on organisation and management
To guarantee the keeping of medical records
To guarantee the access to complaint systems and compensation for patients
To show evidence of explicit and transparent organisation and management rules and practices that include procedures related to the management of cross-border patients in their field of knowledge and expertise
To possess the ability for essential healthcare practices on the event of an unexpected resource failure or to guarantee referral to alternative resources
To demonstrate the ability to keep the stability, technical capacity and skill of the CR through a sustainable planning of management of the human resources and technological updating
To establish a continuous plan on the activities that ensures the sustainability of the CR with a defined time dimension
To guarantee the use of standardised information and recognised codification systems on a national and international scale
To ensure easy access to other resources, units and specific services, necessary for the management of patients through conclusion of agreements with other services or structures that will guarantee the continuity of healthcare (e.g. operating suites, intensive care units)
To ensure the transparency of fees applied to national and foreign patients by the CR
To ensure the capacity for cross-border communication after the patient's discharge
To demonstrate the ability to collaborate with other CR and RER, be it on a national or international scale

Table 5. General criteria pertaining to potential for research and training.

General Criteria related to capacity for research and training
To demonstrate capacity for teaching and training, including those performed by distance-based methods, on academic and specialised levels in the field of competency and experience of the institution
To possess the ability for research on its field of expertise
To demonstrate certified expertise in collabortive research and the participation in European or international research networks

Table 6. General criteria pertaining to information systems.

General Criteria related to information systems
To demonstrate the ability to facilitate national and international mobility of skills, physically or vistuall, through an information system and e-health tools, namely through telemedicine
To demonstrate the use of the best technologies and the best treatment procedures in its field of competency and expertise, based on knowledge and evidence.

At the same time, CR must cumulatively satisfy the following **specific criteria**, based on knowledge, evidence and feasibility in each field of specialisation:

i) Possess competence, expertise and recorded practices;
ii) Show casuistics (indicating the minimum and ideal numbers, by establishing the minimum and ideal ratio of patients per year, according to international patterns);
iii) Show good clinical results, in accordance with the evidence available;
iv) List the type, number, qualifications and competencies of human resources;
v) Describe the organisational and functional prerequisites;
vi) Possess and categorise specific equipment, including e-health tools (so that it will be possible to process, manage and exchange information in image with other practitioners outside the CR);
vii) Guarantee quick access to specific equipment, inside or outside the CR (e.g.: radio-oncology, haemodynamics);
viii) Show evidence of the use of multidisciplinary approaches.

Therefore, the health care provision context is different between each Member State of the European Union, the listed criteria, both general and specific, may be complemented with other criteria, taking into account the internal circumstances of each country, in order to adapt the specific criteria to the RER they intend to join.

Nevertheless, the Ministry of Health, as the national accountable authority, may decide to revoke the recognition of a CR in cases where: (i) one or more prerequisites within the criteria, which form the

foundation for this recognition, are no longer satisfied, or (ii) keeping it in the health system proves to be unnecessary.

It should be noted that no CR located in a Member State may apply to be recognised, on a European scale, as a CR, without complying with the regulation on the matter within the legislation of the Member State of origin and without complying with the criteria and condition demanded so that the CR may become part of the RER.

The general conditions and criteria a CA must comply with to be officially recognised by the Ministry of Health are as follows:

i) To possess a multidisciplinary team practising full-time;
ii) Carry out activities on the preparation of healthcare and/or research practices on an intensive and complementary basis to a CR;
iii) Formally accept technical supervision from the CR in the specific collaboration field.

The process of identification of a CR goes through a number of stages that will be described in the following chapter.

8 REFERENCE CENTRE RECOGNITION PROCESS

Due to the non-existence of official recognition for a CR in Portuguese territory, there will be a need to proceed to the preparation and approval of legal measures that apply, in legal and administrative terms, to CR in Portugal, based on an a priori basis on the Directive.

The following table reflects, in a summarised way, the stages inherent to the aforementioned process.

Table 7. Chronogram pertaining to the creation and approval of legislation on the CR to be established in Portugal.

CHRONOGRAM ON THE ELABORATION AND APPROVAL OF CR CONSTITUTIONAL LEGISLATION IN PORTUGAL				
MACRO DESCRIPTION	MICRO DESCRIPTION	ENTITIES INVOLVED	APPROVING ENTITIES	TIME PERIOD (WEEKS)
Elaboration and approval of laws	Elaboration of legal certificate	Ministry of Health	Ministry of Health	8

In the process of giving recognition to CR on a national scale, there are three head offices for analysis and assessment, to be constituted by decision of the Minister of Health, which will be: (i) Classification Commission, (ii) Technical Specifications Experts Group and (iii) Technical Commission for Assessment.

The **Classification Commission** for the CR must take on the responsibilities of: (i) assessing the demand for healthcare practices and identify the large areas of intervention in which the CR must be founded, (ii) elaborating, justifiably and subject to the intervention area selected, a proposal for pathologies, techniques or technologies the centres will lean on, (iii) defining the ratios of national implementation in accordance with transparent principles revolving around population incidence analysis, accessibility, balance between offer and demand, epidemiology and services available, (iv) approving the general and specific prerequisites the CR must comply with and (v) propose to the accountable entity the decision to give official recognition to the CR candidate centres.

This considered, the official recognition of the CR comprises of numerous stages and requires the involvement of various entities and institutions of the Ministry of Health, which will have to ensure the agility and complete transparency of the process, namely in what concerns the identification of the fields

of specialisation which there may be CR practising and the assessment of the applications to recognition of CR.

The formal proposal for the high specialisation fields in which there will likely be CR practising will be done by the Classification Commission, based on prior diagnosis of the situation, drawn from epidemiological data, production data and the existing resources, so as to make it possible to plan the number of centres taking on the country's demand.

The Classification Commission must also elaborate a model that will reflect the creation and functioning of the CA and will be presented to the authority with high priority.

The **Technical Specifications Experts Group** for the CR will perform in the following stages: (i) identify the minimum prerequisites to be considered in the assessment of the candidate centres and (ii) clarify doubts and validate factors related to the assessment of CR at the request of the Technical Commission for Assessment. This group of experts, highly differentiated, will function on a thematic field basis on technical pathologies, procedures or technologies and should have, for each specific group, one scientific coordinator and one rapporteur. On the matter of **describing the minimum criteria to be considered in the identification of CR**, this group must also define the prerequisites the CR must satisfy, namely:

i) Management and functional rules;
ii) Patient safety procedures;
iii) Unit quality guarantee programme;
iv) Clinical and organisational norms of the Directorate-General of Health and internal functional norms;
v) Minimum output and outcome indicators;
vi) Procedure model and guarantee from internal auditing;
vii) Model for the disclosure of results;
viii) Reports to the patient and family;
ix) Insurance of the patients' rights and liabilities (subject to evaluation of compliance);
x) Continuity of healthcare practices through clinical information on transfer or discharge of the patient.

The identification process of the minimum prerequisites for the assessment of CR and CA must include the audition of the Medical Association.

The **Technical Commission for Assessment** of CR must possess the following competencies: (i) assess, on recorded format, the self-evaluation process, (ii) verify the quality of the proposals submitted, (iii) carry out visits to the candidate units for assessment of all the information sent, (iv) prepare the final report of appreciation of the applications, to be submitted to the Classification Commission and (v) promote an auditing model.

This Commission will also be in charge of overseeing a number of specific prerequisites, namely:

i) The professional expertise of the team performing at the centres, in terms of: (a) minimum and ideal assistance activity, (b) the practitioners' base, continuous, under and post-graduate training, teaching and research activities and (c) multidisciplinary sessions;
ii) Validating the transmission and sharing of knowledge, verified by the publishing of scientific articles, taking part in conferences and the interconnecting with the European counterparts;
iii) Identifying the human resources affected and their suitability to the objectives held by the CR;
iv) Identifying the facilities and equipment needed;
v) Identifying the availability of other services and/or units;
vi) Identifying other articulated healthcare practitioners;
vii) Identifying the patients' clinical record method and the information systems used;
viii) Supervising clinical intervention through the analysis of result indicators;
ix) Defining the minimum summary of data to supervise activity and quality;
x) Identifying protocols and plans of action.

It is under the Classification Commission's charge to **approve the minimum prerequisites**, general and specific.

The **publishing of these minimum prerequisites**, including quality criteria, the recognition of CR is dependent on the responsibility of the Ministry of Health.

The **start of the application process** for CR is the responsibility of the Ministry of Health, which will provide a self-evaluation survey for this purpose. If the applications submitted to a single reference area reach a considerably high number, it will be considered to exclude this same reference area of CR altogether, considering such a scenario could lead to misguidance as to the concept of CR (which are meant to focus mostly on complex or demanding pathologies, diagnosis and treatment of which would benefit from an economy of scale through the concentration of expertise and knowledge).

As previously mentioned, the **analysis and assessment of applications** is the responsibility of Technical Commission for Assessment, together with the eventual Technical Specifications Experts Group. In order to validate the self-evaluation, the information and compliance with the general and specific criteria of CR candidate centres, the Technical Commission for Assessment will carry out **visits to the candidate units**, after which it will be responsible for the **elaboration of a final proposal** of official recognition of CR. The report must be concise and objective, and subjected to review and approval by the Classification Commission.

Lastly, the Classification Commission will submit a list of centre suggestions to the Ministry of Health, which it will approve and thus officialise the recognition of CR, through publication of the approved CR on the Official Journal. The recognition procedure should be valid for a fixed time period, and renewal should be dependent on the reassessment of the centre. It is proposed for a centre to be active as a CR for up to 5 years. The Portuguese points of focus of the Experts Group for the European Commission and the European Committee RER on Cross-border Healthcare must oversee the recognition procedure of CR.

The activity of CR must be subjected to external, independent auditing and preferably involving international experts.

A transition period must also be allowed between the publication of the national legislation mentioned above and the beginning of the activity of the first RER, then making a start on the Portuguese procedure to identify CR for competency areas that cover the most demanding procedures, techniques and pathologies that require a vast field of knowledge, competency and expertise. Even if the identification of the fields of intervention of national CR is under the charge of Classification Commission

as referred below, the identification of the first fields of intervention will, exceptionally and in an initial stage, come down to the Work Group's views. These first few fields the CR primarily focus on, for later approval by the Classification Commission, correspond to the transplantation of solid organs, paediatric cancers, breast cancer, melanoma, haemophilia, rare congenital metabolic diseases, including lysosomal storage disease and the haemodynamic and cardiac intervention procedures.

Table 8. Chronogram representing the stages inherent to the recognition of CR.

CHRONOGRAM ON THE STAGES OF CR RECOGNITION					
STAGE	MACRO DESCRIPTION	MICRO DESCRIPTION	ENTITIES INVOLVED	APPROVING ENTITIES	PERIOD (WEEKS)
1	Defining the priority areas, pathologies, techniques and/or procedures of the Reference Centres and national ratios	Elaborating the diagnosis of the situation and identify the major intervention areas, pathologies, techniques and/or procedures the reference centres will focus on	Classification Commission	n.a.	6
2	Approval of the priority areas, pathologies, techniques and/or procedures	Approval of the priority areas, pathologies, techniques and/or procedures of high specialisation the reference centres will focus on	n.a.	Ministry of Health	4
3	Proposal of specific criteria and pathology, techniques and/or procedure indicators	Identifying the criteria, based on scientific evidence, to consider on pathologies, techniques and/or procedures and assessment of the candidate centres	Technical Specifications Experts Group	n.a.	6
4	Elaborating the proposal of the criteria and respective indicators for the selected pathologies and procedures	Elaboration of the document for higher approval of the soecific criteria and indicators to be used by the Experts' Group	Classification Commission	Ministry of Health	4
5	Beginning of the application process	Submission of applications for Reference Centres	Ministry of Health	n.a.	4
6	Analysis and evaluation of applications	Appreciation and analysis of applications to verify if the candidates comply with the general and specific criteria	Technical Commission for Assessment	n.a.	8
		Documental and local evaluation processing and elaboration of a report with a final proposal for official recognition of reference centres		n.a.	6
7	Report assessment	Analysis of the report elaborated by the Technical Commission for Evaluation and submition of a list of referente centre candidates	Classification Commission	n.a.	4
8	Official recognition of Reference Centres	Ministry decision to officially recognise the Reference Centres	Ministry of Health	Ministry of Health	4
TOTAL ESTIMATED TIME PERIOD FOR THE RECOGNITION OF REFERENCE CENTRES					46

Key: n.a. - non-applicable

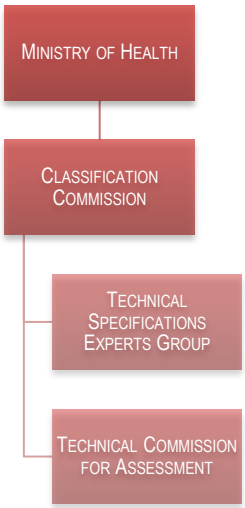

Image 7. Entities involved in the process of recognition of CR.

It must also be noted that, should a centre attain official recognition as a CR, by the Portuguese Ministry of health, the European Commission may dismiss the repetition of the assessment process on a European Union level.

The official recognition of a CA by the Portuguese Ministry of Health demands application with the Classification Commission, on which there must be documentary proof of compliance with the general conditions and criteria established. The Classification Commission will resort to the Technical Commission for Assessment and/or the Technical Specifications Experts Group for evaluation of the proposal for official recognition as presented in the application, which, if positive, will be submitted by the Classification Commission to the authority's decision.

It is suggested that the entire process be carried out by one single entity that will ensure functionality throughout. Taking into account the global and specific competencies of the numerous entities that constitute the Ministry of Health, it is suggested that the Directorate-General for Health is the central entity to lead this process. The complexity of the entire process and its continuity in time argue that the Directorate-General for Health should be provided with the necessary conditions for the future development of this process in a straightforward, agile and transparent model.

Considering the financial weight and the necessary evolution of the financial model, it is relevant to consider the need of a collaboration channel with the Central Administration of the Health System, I.P. (ACSS) for specific ends.

9 GENERAL TEMPLATES FOR THE FINANCIAL MODEL

Within the literature and records consulted on RER and CR, it is stated that by CR one means "*healthcare practitioners, with certified technical knowledge to diagnose and provide high quality healthcare practices to patients with certain clinical conditions that require special concentration of resources and expertise due to the low frequency or complexity or high costs of those same conditions*".

As such, the "statute" of CR may be attributed based on different clinical conditions, be it in terms of frequency or complexity (implying case-by-case analysis of a suitable finance plan), which may translate into pathologies or procedures categorised as:

i) Low frequency diseases — rare diseases (which, apparently, is the path currently being "drawn" on a European scale);
ii) Complex diseases;
iii) Costly pathologies/techniques.

As previously diagnosed in the GTRH Report, it is important to proceed to the identification of CR, in the different hospital entities and regions, in the sense that, when it comes to less frequent diseases, the diagnosis and therapeutics of some pathologies must pass through the concentration of casuistics and resources.

Currently, there are tasks being carried out by the technical group formed under Order No. 9495/2013, of 9 of July of 2013, of the State Secretary of Health, issued in the Official Journal, series II, No. 138, of 19 of July of 2013, its goal, among others, being, "Analyse the suitability of the national, regional and local offer on hospital healthcare to the health demand of the population benefiting from these services," while these tasks must be carried out "as a tight collaboration with the Hospital Reform project team".

This way, the strategic planning process seeks to ensure the coherence of the hospital offer (on a national, regional and local level), namely through the precise definition of the set of services, which, instead of focusing on services themselves, must focus on the constitution of multidisciplinary and flexible teams specialised for the diagnosis and treatment of health conditions, based on the health-related needs of the population and the promotion of patients' safety.

In the context of the constitution of CR for certain pathologies/procedures, the strategic planning process may be constituted as a driving force for the establishment of CR, without loss in keeping community-based healthcare through the constitution of CA that should act in tight collaboration with the CR on the pathologies/procedures these practise on.

9.1 HOSPITAL FINANCE MODEL AND PAYMENT METHODS

The hospital finance model and, more precisely, the payment methods established are, in the health field, one of the available instruments to reach better clinical practices and motivate practitioners to maintain an attitude that will lead to clinical excellence, without compromising maximum efficiency. As such, when considering the suitable payment methods for the assignment of resources to the public hospitals, one may also be considering ways of motivating healthcare practices of excellence in selected centres and pathologies/procedures, meaning one should also discourage the treatment of patients in centres that have not received the statute of CR in a certain area.

In general terms, the following table summarises the usual method through which resources are assigned and the payment methods that have been integrated in the hospital finance model, as well as the level at which the practitioner is encouraged to follow certain practices.

Table 9. Resources assignment mechanisms and payment methods.

INDUCTION OF PRACTICES THROUGH RESOURCE ALLOCATION MECHANISMS AND PAYMENT METHODS				
BEHAVIOUR OF THE PROVIDER / MECHANISMS	AVOIDING HEALTH PROBLEMS	HEALTHCARE PRACTICES	RESPONDING TO THE USER'S EXPECTATIONS	CONTAIN COSTS
Capitation	+++	--	++	+++
Overall Budget	++	--	+/-	+++
Episode	+/-	--	+/-	+++
Charge per day	+/-	++	++	---
Act	+/-	+++	+++	---

Thus, it is possible to draw different payment methods that will more successfully respond to the need to encourage certain behaviour.

In the current model, there are different combinations of payment methods, based on objectives and practices that need encouraging.

Since 2008, Portugal has turned to the development of models for integrated disease management, aiming to improve the integrated and global approach of the patient for some pathologies, in selected CT, applying payment methods per treated patient. These methods are characterised by their main aspects, as follows: (i) definition of the protocol suitable for a patient-type and (ii) establishment of a price per treated patient. These payment methods have come to be applied to clinical conditions of low casuistic and high costs (e.g. Para-amyloidosis, Pulmonary Arterial Hypertension), as well as fields which demand a multidisciplinary treatment and in selected centres, as was the case with surgical treatment of obesity and, currently, in the field of Oncology.

9.2 UNDERLYING PRINCIPLES OF THE FINANCING AND CONTRACTING OF REFERENCE CENTRES TO BE CONSTITUTED IN PORTUGAL

In conformity with what has been achieved to this point, both in what concerns the more explicit per treated patient payment methods and the remaining payment methods coexisting in Portugal, there may be numerous scenarios deemed suitable to answer to the goals of reimbursing rare and demanding pathologies, how to reimburse complex pathologies and procedures for which the treatment of the patient implies going through numerous courses of activity. This means payment methods must be studied case by case to find one that best suits the CR that may be constituted in Portugal, in conformity with the inherent aims of their constitution.

Regardless, and considering the goals listed in this document concerning the selection of CR in Portugal, the inherent principles to the financing and contracting of healthcare must be as follows:

i) Whatever the fields the constituted CR may focus on, their coverage capacity must be assured on a national level for the treatment of pathologies and procedures considered;
ii) Within the fields for which CR have been established, healthcare contractual relations may only resort to the CR established for the pathologies and procedures considered;

iii) In the fields where there are CR established, it must be ensured that only those CR may be financed for the production in that field, that is, payment methods will only apply in the fields of reference for these CR, meaning there will be no financing assigned to pathologies and procedures considered in other institutions;

iv) In the fields where there are CR established, a set of healthcare practices to be offered in other institutions (CA of CR) must be defined when supervising a patient, and in which case there should be financing assigned to these institutions, in conformity with the practices they will be responsible for.

v) When defining the financing for CR and CA, not only for performance in assistance but also in teaching/training and research must be properly included.

The entire model established on the premises previously presented will demand, besides the establishment of fields of reference and listing of the treatment performed, the definition of community-based centres and the establishment of community-based/continuous healthcare practices that will be placed in a different class to the CR (these centres may eventually be classified as CA of CR for fields ultimately considered fields of reference).

10 MERGING OF REFERENCE CENTRES WITH THE PORTUGUESE HOSPITAL NETWORK

The Portuguese Hospital Network is formed by a group of public hospitals mostly organised into hospital centres or local health centres.

In general terms, the Portuguese hospital units, as well as medical training are organised into service units according to the medical and surgical specialisations defined by the Medical Association.

Of the few medical specialisations existent a few years ago, there are currently 47 specialisations, 17 sub-specialisations and 8 competencies in Portugal, and numerous categorising methods have been created in order to establish different organisational models. Generally, the current organisational model is based on large anatomo-functional systems and only in a few, very particular, cases does it go deep enough to reach the level of specialised pathologies/procedures. This is, however, still a very fragile reality, with only some materialisation in the creation of functional units or centres of interest.

The diagnosis and therapeutics of the most distinguished medical and surgical pathologies, especially the less frequent ones, require a special treatment that will undoubtedly involve the concentration of casuistics and resources, with multidisciplinary teams, with a much stricter control and a large weight on research and teaching.

CR then represent a new collaborative model between medical specialisations, with its own functioning rules and payment methods, in order to achieve the goals they have set out for. As previously mentioned, the CR must form a pyramid hierarchy of differentiation and multidisciplinary approaches, following with the CA, in terms of differentiation.

This means two realities coexist within the Portuguese SNS: hospital services organised in differentiation networks and mixed CR that may be constituted as highly differentiated and multidisciplinary centres as part of numerous networks.
This way, it is clear how important it is to knit, in a structured manner, healthcare practices together through inputs from the RRH and the creation of CR, which may become part of the RER themselves.

Likewise, these new concepts bring along the need to rethink the formative model in the sense that the concentration of pathologies will hold mandatory implications.

The merging of the hospital network and the CR should form a dynamic and progressive process.

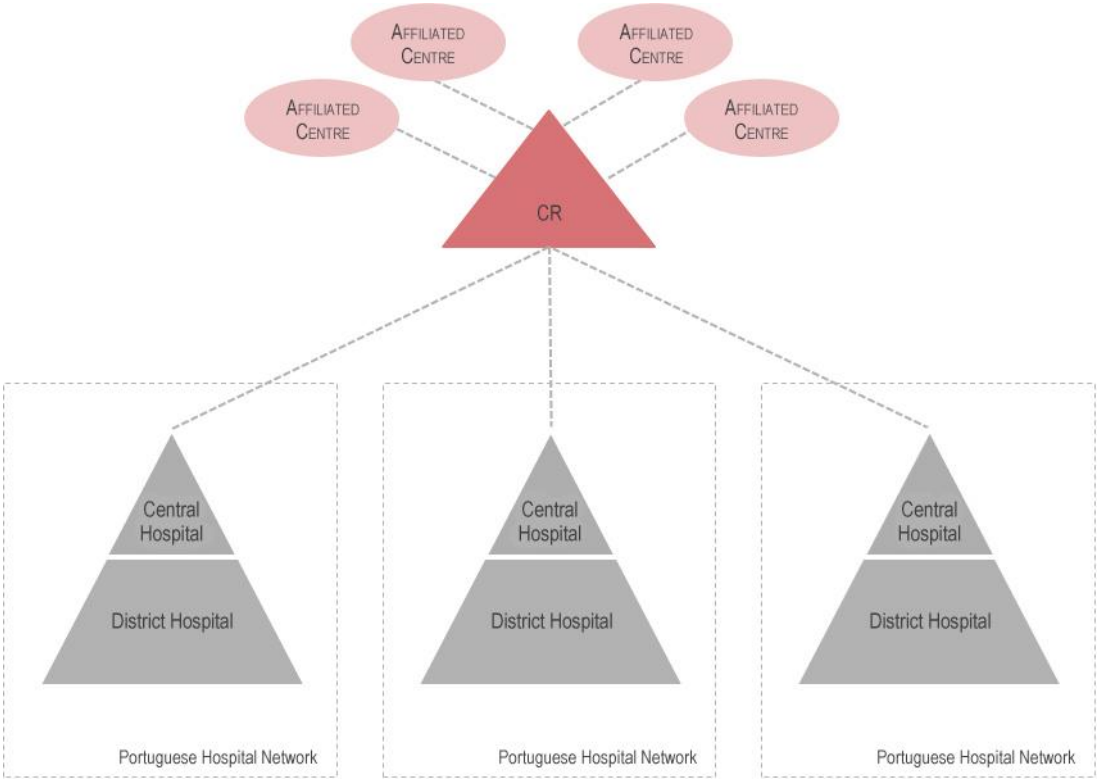

Image 8. Merging model for CR and the Portuguese hospital network.

It is imperative to initiate this process in order to guarantee a proper articulation between services and the patient flow in an organised manner, allowing for healthcare practices with better accessibility and effectiveness. Similarly, the currently progress process to elaborate strategic plans implies the structured and recorded development of the entire process without which it won't be possible to design proper healthcare planning.

11 EUROPEAN REFERENCE NETWORK

The European Commission defines the concept of **European Reference Network** as a network of CR providing highly specialised healthcare practices and unifying a special concentration of resources and competency and expertise, based on healthcare practices of excellence, accessible and cost-effective, and which may form a focal point not only for medical training and research, but also for the circulation of information, knowledge and assessment.

The RER aim to promote the cooperation between Member States in specific fields where economies of scale, a result from coordinated action, may bring a significant an added value to the national health systems and thus contribute to the improvement of accessibility to high quality healthcare offer and safety, more so for patients with pathologies that require a higher concentration of resources and expertise.

According to the state-of-the-art, based on international scientific evidence, there is a positive relation between: (i) the frequency and the expertise when performing a certain treatment or procedure and (ii) the quality of its results. Considering that highly specialised healthcare requires a significant investment of structural, human and technical resources, which in turn demands a dynamic and continuous update of knowledge and technologies, as well as the existence of a sharing chain to verify the efficiency and the coordination of resources and knowledge and expertise, there will be obvious benefits both for the patients and the health systems by reducing the differences in quality and results in healthcare. To achieve this, top management and strategic planning play vital roles within the health system, as it may be necessary to proceed into the reengineering of the network and healthcare practices, namely when it comes to concentration, be it in terms of casuistics or resources.

According to No. 2, of article No. 12, of the Directive, each RER must honour, at least, three of the following goals:

i) Ensuring the potential of the European cooperation founded in highly specialised healthcare practices for the patients and health systems, based on medical innovation and that of the technologies of health;
ii) Contributing to the circulation of knowledge concerning disease prevention;

iii) Promoting the improvement of diagnostics and high quality healthcare practices, accessible and cost-effective for all patients with a specific need of concentration of competence and expertise;
iv) Maximising the cost-effectiveness based on a concentration of resources, when appropriate;
v) Strengthening research and epidemiologic vigilance through shared records by the RER and the training of health professionals;
vi) Collecting, exchange and circulate knowledge, evidence and expertise, virtually or physically, in and outside of the RER, on the different alternatives on therapeutics options;
vii) Fostering quality and safety, by circulating the best practices in and outside the network;
viii) Assisting Member States that hold insufficient casuistics and lack a certain type of technology or expertise, providing highly specialised services marked by outstanding quality.

Since the RER are based on the voluntary participation of the CR and their Member States, these must manifest their compromise in following, supporting, contributing to and taking part in the activities and the work procedures of those same RER, in conformity with the legislation of the Member State they belong to and the conditions, criteria and procedures of the Network they are applying to.

With that in mind, and in accordance to No. 4 (a) of article No. 12 of the Directive, A RER must satisfy the following conditions and criteria:

i) To possess knowledge and expertise to diagnose, perform a follow-up and manage patients with proof of good results;
ii) To adopt a multidisciplinary approach;
iii) To offer a high level of expertise and skill to produce recommendations of good practices, applying quality and results control measures;
iv) To contribute to collaborative research, within the RER and the European Union;
v) To promote training activities;
vi) To collaborate with competency and expertise centres in other networks on national and international scales.

On top of the criteria listed in the Directive, a RER must also satisfy the following prerequisites:

i) To provide high quality levels and security;

ii) To identify and promote multidisciplinary counselling in complex cases;

iii) A clear mutual accountability with the patients;

iv) To support healthcare practitioners in their field of study and expertise, in order to raise their local, regional and national capacity for healthcare practices.

The European Commission is considering the following criteria and conditions to be applied to each of the future RER:

i) To possess suitable knowledge and advanced specialisation to diagnose, treat, supervise and manage diseases and patients, in accordance with evidence and the achievement of good clinical results:
   a) Possessing a high level of quality in healthcare practices applied to certain diseases or clinical conditions, as well as safety for the patients, through a suitable diagnosis or management of the disease;
   b) Further enabling and involving the patients, in order to strengthen healthcare quality and safety.

ii) To adopt a multidisciplinary approach:
   a) Identifying the domains and the best approaches for multidisciplinary work;
   b) Assisting and promoting multidisciplinary counselling in complex cases.

iii) To dispose of a high level of specialisation and expertise and to possess skills to elaborate guidelines on good practices, establish measure based on results and ensure quality control:
   a) Exchanging, collecting and promoting the circulation of knowledge, evidence and expertise in and outside the RER, especially on different alternatives and the best practices related with diagnoses and treatment;
   b) Supporting the expertise of the CR, so as to improve their specialised capacity;
   c) Establishing guidelines for good clinical practices;
   d) Establishing indicators for performance and results;
   e) Maintaining a quality and safety management and evaluation system for the patients.

iv) To contribute to the development of research:
   a) Identifying and approaching gaps in the field of research;

b) Promoting the collaborative research within each RER, creating a solid structure and providing technical support to the conception and establishment of research projects I the European Union;
c) Reinforcing research and epidemiologic surveillance through the creation of shared records in each RER.

v) To organise education and training activities:
a) Identifying and approaching gaps in teaching in the specific practice field of each RER;
b) Promoting teaching and continuous training programmes in the specific practice field of each RER.

vi) To keep a close collaborative partnership with the CR and other RER on a national, European and international scale:
a) Exchanging and promoting the circulation of knowledge and good practices by the CR;
b) Creating network based work, through communication tools, clinical protocols, clinical information exchange and training and coordination models.

vii) To make the use of cost-effective resources easier:
a) Promoting the concentration of resource where appropriate, used for clinical conditions of high complexity and low frequency or incidence;
b) Analysing the feasibility and the evidence concerning treatment value and potential so that positive clinical results will be obtained.

The criteria and conditions required for the CR of Member States to become part of the RER and be recognised as CR on a European level make up the foundation for the establishment and assessment of the RER. The development of RER is a responsibility shared by the Member States on a national level and by the European Commission. In conformity with this, the RER may adopt new CR applying to join, so long as the general criteria applicable is respected. The participation of CR within RER, as previously mentioned, is voluntary and implies the acceptance on the part of those CR of the criteria and conditions established on a European level and showing they abide with the criteria and conditions established by the national legislation of the Member State of origin, thus receiving permission, as previously referred, to use a specific European logo, adopted and registered by the European Commission.

For the constitution of a RER, the following are the minimum details on administration and coordination to be clarified: (i) the RER Coordinator, voted for by the representatives of the merged CR; (ii) the RER Council; and (iii) the representatives of each of the CR merged with the RER.

The RER **Coordinator** will be in charge of coordinating activities and lead the Network Council. The specific tasks and responsibilities of the Coordinator, as well as the rules for this position and nomination, will be defined during the Implementation Act on the establishment of the Network by the European Commission or in the internal regulation of the RER itself. The Coordinator, assisted by the Network Council, will support and facilitate the internal coordination of the RER, as well as its cooperation with CNA.

The Coordinator of each RER must demonstrate professional training and expertise relevant to the field of study and expertise of the Network and be a member of the team of one of the CR in the European Union, receiving the support of the administration of the CR they belong to, in conformity with the internal provisions applicable in their Member State.

The **Council**, led by the Coordinator of the RER and, preferably, formed by one representative of each CR comprising the RER, will function mostly as a management and support team, bearing the responsibility, broadly speaking, for the elaboration of operating rules, annual and multi-annual work plans, goals and progress reports for the activities of that RER. In terms of specific duties, as well as the functions and work procedures of the Council, these will be clarified in the respective Implementation Act of the European Union and/or in the internal regulation of the RER.

Each CR must formally assign a **representative** to take part in the RER with the following roles: (i) representing the Centre within the Network, (ii) maintaining the connection between the Network and the Centre, (iii) taking part in the Network Council and (iv) collaborating and holding council with the Network Coordinator, in all kinds of matters related to the competency and expertise field and coordination of the Network.

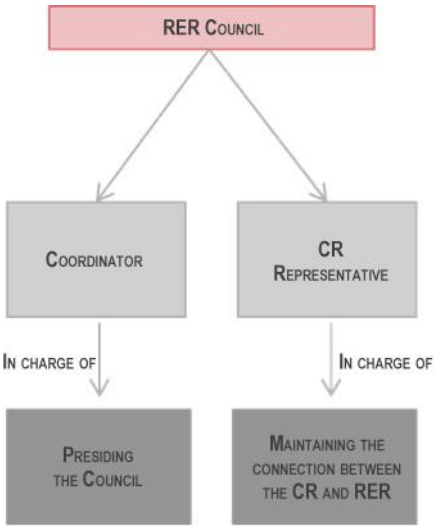

Image 9. Governance and coordination elements in the RER.

The RER will operate on a daily basis, providing structural and operational support for the CR that comprise them, based on common tools and solutions pertaining to information technologies and e-health, depending on the establishment of:

i) Solutions shared in the fields of telemedicine, namely through image, data and sound live transmission, information storage and relay, so as to maximise an efficient use of resources, simultaneously allowing the effective exchange of clinical information between professionals, as well as the examining and evaluation of the patient for diagnosis and supervision;

ii) Compatible systems in the fields of information technologies, ensuring the interoperability and the semantics, concerning the exchange of clinical data and information on the patients;

iii) Systems and solutions in the fields of information of technologies related to the creation and maintenance of shared data and record bases.

12 SHORT AND MEDIUM-TERM EUROPEAN PERSPECTIVE

The article 12.4 of the Directive determines that the Commission should support RER's development. Therefore, the article 12.4 (a) requires the Commission to adopt a Delegated Act, establishing the criteria and conditions RER should observe, as well as the conditions and criteria required to health care providers who intend to join these networks. On the other hand, the article 12.4 (b) and (c) requires the Commission to adopt an Implementation Act including the criteria to establish and assess those RER, as well as the instruments to facilitate the exchange of information and knowledge and for establishing and assessing these networks, so that the members joining them may cooperate among themselves in a particular field of expertise.

The Directive further establishes that any health care provider in a Member State, in order to become member of a RER, must comply with the legislation of the Member State where he is established, and with all pre-established criteria and conditions set out by the Commission through the Delegated Act.

Although there is no deadline for adopting the Delegated Act and Implementation Act, we expect the Commission to simultaneously adopt both acts, in March 2014, and through two Decisions, whereas the Commission and Member States have been working together towards this since January 2012.

In what concerns the Delegated Act, the Commission's services prepared a non-official list with the criteria and conditions required by the article 12.4 (a), whose content was discussed by the cross-border health care experts group, formed by the State Members' national representatives, taking into account the contributions collected by the public consultation carried out by the Commission, the visits to the State Members and the several meetings held with experts.

As for RER's Implementation Act, in order to comply with the mandate set out by the article 12.4 (b) and (c) of the Directive, the Commission will establish the criteria and conditions, clear and strong, for establishing the RER, identifying its members and assessing the networks, so that they provide added value in European terms, already recognized by the co-legislators of the Council and European Parliament when adopting the Directive.

The Member States and the Commission shall be responsible for the RER's development, through the mutual cooperation and collaboration at European Union level.

Any RER, or member part of it, should be identified, selected and assessed according to clear, open and transparent procedures.

The process leading to the establishment of a RER and to the identification of its members, shall be based on a strong technical assessment, performed by an independent entity which will decide if the aspiring members of a RER observe the criteria pre-established by the Delegated and Implementation Acts. The selection by the Commission of an "independent body" in order to assess RER and their members will comply with a competitive and transparent process. We expect this "independent body" to be formed by October 2014.

On the other hand, the article 12.3 of the Directive states that the Member States should facilitate RER development, connecting specialized centres in national territory and ensuring the dissemination of relevant information to promote its integration within RER.

The Commission, after approving both legal acts – Delegated and Implementation – and officially disclosing both Decisions, will open the proposals process for RER, expected to occur in February 2015. Consequently, the Member states should be prepared to apply their CR to join the future RER.

The CR intending to join a RER, having the agreement from their home Member State, should express their commitment to participate within the network's activities, according to their criteria and conditions during an initial period of five years.

The technical assessment of RER's proposals and members who will join them, will be performed by the "independent body", with head office in the Commission, according to clear and explicit assessment rules. The assessment rules will be explained in an "assessment guide", which will include the specific assessment methods, besides an extensive review of the documents and the result from local audits. The "independent body" shall conclude the work with a technical assessment report to identify the networks and CR complying with the assessment criteria. Only with a positive assessment from the "independent body" will it be possible to establish a RER and accept a CR in that network, whose disclosure will be made by the Commission.

After commencing the activity, each RER will be assessed according to their results, as well as their members. The expected results of a network as a whole, as well as the results expected from each member, should be clearly assessed. The process for carrying out this assessment will be concluded with an assessment report, positive or negative, made by the "independent body", including a recommendation to the Commission regarding the continuation of that RER or its members. Only a positive assessment report will enable the network to continue. In the event of a negative assessment report, a grace period of one year may be granted for correcting the detected flaws, as long as an improvement plan is presented. In the absence of this improvement plan, the negative assessment will lead to the extinction of the network or any of its members. The "independent body", in coordination with the Member states' competent authorities, will draft a second assessment report at the end of each grace period, determining the continuation or not of the network or its members.

We expect the establishment of the first RER to occur in 2015.

13 PRIORITY INTERVENTION AREAS

Currently, it is important that Portugal starts as soon as possible the process for establishing CR and defines some priority intervention areas. In fact, that same effort is being made in other European countries.

So, the GT considers to propose some priority intervention areas for establishing CR. These areas will constitute the first phase of the CR's creation, and follow the process as legally approved. We suggest that this first phase is particularly audited and assessed so that it becomes possible to facilitate the creation of new CR in forthcoming phases. Considering the foreseen European calendar, we expect the conclusion of this first phase by 2014 and a new phase to start also in the same year.

The GT also considers that an annual routine should be created, enabling to ensure in due time the definition of new CR development areas, as well as the necessary financing for that purpose.

In this path, and with reference to the European tendency for its constitution in high complexity and expensive areas in which the concentration of resources is cost-effective, as well as the priority areas assumed therein, taking into account the principles established in the PNS, we hereby propose the following areas to be included in the first phase of CR creation:

- Transplantation of solid organs;
- Oncology;
- Inherited metabolic diseases;
- Haemophilia;
- Haemodynamics and intervention cardiology.

In the specific case of **solid organs transplantation**, the high complexity results in the need to allocate human and material resources, and also in the need to organize services targeted to collect and transplant, which, in GT and experts' point of view, justifies the consideration as intervention priority area.

In Portugal, the need to transplant solid organs is clearly covered. In this path, and considering the compliance with the general and particular criteria of the CR, the solid organs transplantation area is a

good candidate to CR in Portugal. Like in other countries, such as Spain and Italy, the transplantation is a field with innate potential not only for contributing to the enrichment of the national health care provision network, but also for establishing bilateral arrangements and being an attraction for health care provision with high quality and security.

In the case of **oncologic diseases**, several factors contribute to their consideration as another area with high potentiality for developing the first CR in Portugal, namely the fact that cancer is the main cause of death before 70 and the second cause of death among all ages in the country. Further, the existence of a health priority programme – the National Programme for Oncologic Diseases – which foresees the development of a reference network in effective oncology, making the existent resources profitable, promoting the knowledge movement and share of different technical and technological means, contributes to choose these pathologies. Consequently, and since the complexity of the treatments involved and the disease-related costs, it implies the setting up of multidisciplinary teams highly qualified and with proven knowledge and expertise, the concentration of resources in particular oncologic diseases becomes vital, following the European tendency of creating CR in oncologic fields.

In what concerns **haemophilia** and **inherited metabolic diseases**, their classification as rare diseases, the high associated disease burden, limited casuistics and costs of the associated treatments, justify, in the Work Group's point of view, the concentration of resources in CR as insurance of the most cost-effective as possible care provision.

Cardiovascular diseases represent a large weight in mortality causes in Europe. Even with a reduction in mortality rate due to cardiovascular diseases in Portugal, mainly because of the advances for treating some clinical situations (such as acute myocardial infarction), circulatory system diseases still are the main cause of death in the country.

The complexity and development associated with percutaneous techniques for diagnosis and cardiovascular therapies presume a health care provision with high quality level, ensuring the compliance with the effectiveness and safety criteria. Throughout the last decades, cardiac diseases diagnosis and invasive techniques have been suffering a remarkable expansion and technological improvement, reflecting better results, namely at organizational level, enabling an early response to pre-

hospital emergency. Portugal has been following this technological evolution, whereas the most sophisticated cardiology intervention techniques are currently available for most people, namely **haemodynamics and intervention cardiology**. Therefore, taking into consideration the predominance of cardiovascular diseases and high mortality rates associated with them, it becomes important to favour the haemodynamics potentiality, making different centres available at national level.

It becomes essential to guarantee that the process for establishing CR in the proposed areas is carried out as soon as possible, so that Portugal is alongside other Member States at the level of development, constitution and formalization of CR, enabling their future integration in RER, establishing itself as a potential agent in care provision services and not only a simple reference in cases for other candidate countries.

This first phase should precede new phases to be established by higher bodies so that Portugal is able to make progresses in the creation of CR and in the differentiation in approaching less frequent and complex diseases.

13.1 TRANSPLANTATION OF SOLID ORGANS

Transplantation has been established as a field of medicine with costs, with limited casuistics (for most of organs) and great complexity, implying a special concentration of human and technological resources, marked by a high risk-benefit relationship. Therefore, it becomes essential that the organization of a transplantation national system, with high quality and organizational standards, is based on highly qualified multidisciplinary teams, with proved knowledge and expertise, and on differentiated and innovative medical treatments and technologies, in order to minimise risks and increase the benefits associated with the organs transplantation, namely solid organs.

The organs transplantation is presented as a treatment with better cost-effectiveness relationship at the level of end-stage renal failure, being the only available treatment in cases of end-stage failure of some organs, such as liver, lungs and heart.

In order to rationalize and improve resources, ensuring high quality and safety standards, it is necessary to ensure the concentration of casuistics and resources and, therefore, promoting the increase of efficiency level in Portuguese health system. In order to achieve this, it is essential to monitor the activity and assess the results from each transplantation centre on a yearly basis. Taking into consideration the eventual need to, in some cases, decrease and increase, in other cases, the existent transplantation units given the people's need, the following quality and safety criteria, considered major criteria, should be considered among others selection criteria:

i) Number of transplants made and teams' expertise;

ii) Clinical results and survival of patients and grafts, ascertained by teams external to the units.

The methodology used for estimating the needs in terms of national units for transplanting solid organs was based on: international ratios and (ii) analysis of the activity, between 2009 and 2012, of the main Portuguese transplantation centres at the SNS level.

13.1.1 KIDNEY TRANSPLANT

The complexity of a kidney transplant, generally grossly comparable to all kinds of transplant, is associated with the number of patients and their proximity and need of daily care regarding techniques for replacement of function. The transplantation centres include a specialized medical field for studying patients with end-stage kidney failure in order to include them in a plan of techniques for replacing kidneys (haemodialysis or peritoneal dialysis), the study and application to a transplant waiting list, the exact moment of the transplantation and immediate surgical care, medical follow-up for the rest of life, immunosuppressive medication management, complications' management and back to the beginning in the event of graft failure.

Presently, there are 8 units for kidney transplant in Portugal, 6 of them with living donor programme, corresponding to one unit with living donor programme per 1.75 million inhabitants and one transplant unit with deceased donor per 1.33 million inhabitants. In production terms, in 2012 there were 40.63 kidney transplants per million inhabitants, whereas 17,641 patients are under renal replacement

therapy. We further highlight that 1977 patients were included in an active list for kidney transplant on December 31, 2012.

Table 10. Kidney transplant per million inhabitants in 2011.

Kidney transplant per million inhabitants – 2011				
Country	**Population (million inhab.)**	**No. of units**	**No. of units/population (per million inhabitants)**	**Transplant rate (no. of transplants per million inhabitants in 2011)**
France	65.1	44	0.68	45.7
Germany	81.8	41	0.50	34.8
Italy	60.8	43	0.71	28.8
Spain	47.2	44	0.93	52.9
United Kingdom	62.3	26	0.42	44.2
Portugal	10.6	8	0.75	45.7
USA	313.1	239	0.76	56.2

According to Italy's Health Council, considering the structural, technological and organizational requirements necessary for a kidney transplant, there should be one kidney transplant unit per 2 million inhabitants, performing at least 25 transplants per year. According to the information disclosed by Spain's National Organization of Transplants, there should be one unit of kidney transplant for adults per 1.5 million inhabitants, with an activity level of at least 40 transplants per year; and one paediatric unit per 10 million inhabitants, with 25 transplants during the last 5 years.

According to the *International Registry of Organ Donation and Transplantation* (IRODaT), the worldwide average is 0.4 kidney transplants per million inhabitants. The current situation in Portugal is 0.8 transplantation units per million inhabitants. So, when comparing countries and the current situation of the country, we suggest that the ratio should be maintained until assessing the results' quality, being the proportion between the number of transplants per million inhabitants and the number of units in favour of the latter, in Portugal's case.

13.1.2 LIVER TRANSPLANT

Portugal has 3 liver transplant units, 2 of them with living donor programme. We estimate that there is one unit per 3.52 million inhabitants. In 2012, the production represented 17.80 transplants per million inhabitants.

Table 11. Liver transplant per million inhabitants in 2011.

Liver transplant per million inhabitants – 2011				
Country	**Population (million inhab.)**	**No. of units**	**No. of units/population (per million inhabitants)**	**Transplant rate (no. of transplants per million inhabitants in 2011)**
France	65.1	23	0.35	17.9
Germany	81.8	24	0.29	14.7
Italy	60.8	22	0.36	17.0
Spain	47.2	25	0.53	24.1
United Kingdom	62.3	7	0.11	12.2
Portugal	10.6	3	0.28	20.7
USA	313.1	133	0.42	20.3

According to Italy's Health Council, for liver transplantation, there should be one unit per 4 million inhabitants performing at least 15 transplants per year. On the other hand, according to the information disclosed by Spain's National Organization of Transplants, there should be one unit of transplant per 10 million inhabitants, with an activity level of at least 35 transplants per year in adults (with an acceptable limit of 25 transplants per year) and 25 paediatric transplants during the last 3 years.

According to IRODaT, the worldwide average is 0.3 transplantation units per million inhabitants. The current situation in Portugal is also 0.3 transplantation units per million inhabitants. When comparing countries, we suggest that the annual ratio of 0.3 units should be maintained. In this case, an exception is made because there is only one paediatric centre that, due to lack of logistics, material or human resources, even limited in time, undermines the programme given the lack of options, like in the past. So, we suggest that there might be differentiation from another centre with expertise in transplantation in adults for paediatric area.

13.1.3 PANCREAS TRANSPLANT

There are 2 units of pancreas transplant in Portugal, representing one unit per 5.28 million inhabitants. At the activity level, in 2012 there were 1.9 pancreas transplants per million inhabitants, whereas 35 patients were in active list for transplant on December 31, 2012.

Table 12. Pancreas transplant per million inhabitants in 2011.

Pancreas transplant per million inhabitants – 2011				
Country	**Population (million inhab.)**	**No. of units**	**No. of units/population (per million inhabitants)**	**Transplant rate (no. of transplants per million inhabitants in 2011)**
France	65.1	16	0.25	1.1
Germany	81.8	23	0.28	2.1
Italy	60.8	13	0.21	1.0
Spain	47.2	13	0.28	2.4
United Kingdom	62.3	11	0.18	3.8
Portugal	10.6	2	0.19	2.4
USA	313.1	112	0.36	3.5

Spain's Transplants National Organization does not specify the number of pancreas transplant units per million inhabitants, however the Organization mentions that the units must register activity in the last 5 years with at least 30 transplants during that period.

According to IRODaT, the worldwide average is 0.2 transplantation units per million inhabitants, a ratio very similar to Portugal. When comparing countries, we suggest that the current ratio of 0.2 should be maintained.

13.1.4 HEART TRANSPLANT

Portugal has 4 heart transplant units, that is to say, one unit per 2.64 million inhabitants. In 2012 there were 2.8 transplants per million inhabitants. On December 31, 2012 there were 42 patients in active list for heart transplant.

Table 13. Heart transplant per million inhabitants in 2011.

Heart transplant per million inhabitants – 2011				
Country	**Population (million inhab.)**	**No. of units**	**No. of units/population (per million inhabitants)**	**Transplant rate (no. of transplants per million inhabitants in 2011)**
France	65.1	26	0.40	6.3
Germany	81.8	22	0.27	4.5
Italy	60.8	19	0.31	4.6
Spain	47.2	18	0.38	5.0
United Kingdom	62.3	7	0.11	2.4
Portugal	10.6	4	0.38	4.4
USA	313.1	129	0.41	7.5

According to Italy's Health Council, for heart transplantation activity, there should be one transplant unit per 3.5 million inhabitants performing at least 15 transplants per year. According to the information disclosed by Spain's National Organization of Transplants, there should be one unit of heart transplant for adults per 4 million inhabitants, with an activity level of at least 20 transplants per year (with a tolerable limit of 15 transplants per year), and one paediatric unit per 12 million inhabitants, with 8 transplants during the past 5 years.

According to IRODaT, the worldwide average is 0.3 transplantation units per million inhabitants. The current situation in Portugal is 0.4 transplantation units per million inhabitants. When comparing countries, we suggest that the number of centres should be adjusted to the ratios average found for 0.3, reflecting in the closure of a unit.

13.1.5 LUNG TRANSPLANT

Portugal only has one unit of lung transplant in the SNS, with 1.3 transplants per million inhabitants in 2012. On December 31, 2012 there were 28 patients in active list for lung transplant.

Table 14. Lung transplant per million inhabitants in 2011.

Lung transplant per million inhabitants – 2011				
Country	**Population (million inhab.)**	**No. of units**	**No. of units/population (per million inhabitants)**	**Transplant rate (no. of transplants per million inhabitants in 2011)**
France	65.1	13	0.20	5.0
Germany	81.8	14	0.17	4.1
Italy	60.8	13	0.21	2.0
Spain	47.2	7	0.15	4.9
United Kingdom	62.3	6	0.10	3.1
Portugal	10.6	1	0.09	1.7
USA	313.1	64	0.20	5.9

According to Spain's National Organization of Transplants, there should be one unit of lung transplant per 7 million inhabitants, with an activity level of at least 20 transplants per year, with a tolerable limit of 15 transplants per year.

According to IRODaT, the worldwide average is 0.2 transplantation units per million inhabitants. The current situation in Portugal is 0.1 transplantation units per million inhabitants. So, and when comparing countries, we suggest that the current ratio should be reviewed to 0.2 or, if financially inadequate, maintaining international arrangements in this field, particularly with Spain.

13.2 ONCOLOGY

Table 15. Cancer - estimated incidence, mortality and prevalence (without gender distinction) for 2008 in Portugal.

Cancer	Incidence			Mortality			5-year prevalence		
	Number	(%)	ASR (W)	Number	(%)	ASR (W)	Number	(%)	Prop.
Lip, oral cavity	1025	2.4	5.8	341	1.4	1.8	2681	2.3	29.7
Nasopharynx	110	0.3	0.7	55	0.2	0.3	345	0.3	3.8
Other pharynx	443	1.0	2.8	325	1.3	2.0	865	0.7	9.6
Oesophagus	634	1.5	3.5	607	2.5	3.2	716	0.6	7.9
Stomach	2889	6.7	13.7	2423	10.0	10.4	4814	4.1	53.3
Colorectum	6952	16.1	31.4	3691	15.2	14.6	19126	16.3	211.6
Liver	477	1.1	2.2	487	2.0	2.1	407	0.3	4.5
Gallbladder	392	0.9	1.6	302	1.2	1.2	522	0.4	5.8
Pancreas	807	1.9	3.7	1064	4.4	4.5	524	0.4	5.8
Larynx	612	1.4	3.5	416	1.7	2.2	1833	1.6	20.3
Lung	3288	7.6	16.4	3319	13.7	15.8	3771	3.2	41.7
Melanoma of skin	799	1.8	4.7	219	0.9	1.1	2905	2.5	32.2
Breast	5333	12.3	60.0	1537	6.3	13.5	21272	18.2	451.7
Cervix uteri	949	2.2	12.2	346	1.4	3.6	3097	2.6	65.8
Corpus uteri	852	2.0	7.7	199	0.8	1.4	3003	2.6	63.8
Ovary	529	1.2	5.3	389	1.6	3.2	1307	1.1	27.8
Prostate	5140	11.9	50.1	2021	8.3	15.2	19440	16.6	449.2
Testis	127	0.3	2.3	22	0.1	0.3	481	0.4	11.1
Kidney	691	1.6	3.8	347	1.4	1.4	2130	1.8	23.6
Bladder	1935	4.5	8.5	721	3.0	2.5	5915	5.0	65.4
Brain, nervous system	989	2.3	6.3	753	3.1	4.3	1142	1.0	12.6
Thyroid	635	1.5	4.8	66	0.3	0.3	2739	2.3	30.3
Hodgkin lymphoma	232	0.5	2.1	51	0.2	0.3	742	0.6	8.2
Non-Hodgkin lymphoma	1476	3.4	8.0	697	2.9	3.1	3934	3.4	43.5
Multiple myeloma	459	1.1	2.1	470	1.9	1.9	1009	0.9	11.2
Leukaemia	1087	2.5	6.5	784	3.2	3.7	2426	2.1	26.9
All cancers excl. non-melanoma skin cancer	43284	100.0	223.2	24302	100.0	106.3	117186	100.0	1296.8

Incidence and mortality data for all ages. 5-year prevalence for adult population only.
ASR (W) and proportions per 100,000.

Source: http://globocan.iarc.fr

There are around 45,000 new cases of cancer in Portugal every year and 24,000 deaths per year. The foreseeable development for the next ten years points out an increase of 12% of new cases, which, in line with the improvement of results and increasing complexity of treatments, forecasts a significant increase of the assistance levels and costs involved for treating these patients.

The asymmetrical results of treating patients with cancer has been discussed and recognized at international level. Several factors have been pointed out as the reason for this difference, namely personal or institutional casuistics, human skills and technical possibilities. The main driver of differentiation emerges from the surgery, therefore most literature refers to patients' ratios regarding patients who underwent surgeries and not treated patients.

In surgical oncology, this matter has been subject of several publications and subject to public policies of care centralization within the pathologies of this field, namely in situations where asymmetries are significant, both in procedure-related mortality and in overall survival and site relapse rate.

Thus, the GT defends that Portugal may adjust the best international practices targeted to centralize the treatment of some pathologies, in order to boost equity of results available to patients.

According to DGS, testicular, hepatobiliary, pancreatic, rectal, oesophageal, stomach, breast, melanoma and paediatric cancers should be considered priority in a first phase of concentration in multidisciplinary treatment.

The number of cases submitted to surgery in each of these pathologies should be studied and, based on that data, the number of centres to open in the country should be established. The second step is defining their geographical dispersion and the minimum number of cases that should be treated annually.

Also, hopefully and according to the current state of art, there is a possibility to create CR treating more than one pathology at the same time, taking into consideration the similarities between organs. For example, it makes sense having the same CR for oesophageal cancer and stomach cancer, as well as for hepatobiliary cancer and pancreatic cancer.

13.2.1 TESTICULAR CANCER

As for testicular cancer, there are around 130 new cases every year in Portugal. The relationship between surgical morbidity and the amount of surgeries is well known in this area in particular. In Portugal, the results obtained in this pathology are a matter of concern, mostly because of its potential cure and early age of affected patients. The sub-optimal results may involve multiple factors, but the multidisciplinary nature of this pathology's treatment, its rarity and importance of surgical capacities, the centralization of these patients' treatment is recommended and urgent.

In United Kingdom, in the context of the programme to improve results in urological cancer, the existence of a centre for at least two million inhabitants for treating testicular cancer was recommended.

13.2.2 HEPATOBILIARY CANCER

In the case of hepatobiliary cancer, published studies are equally in favour of the importance to centralize the treatment of this pathology. In this group, besides primitive tumours, we usually include metastatic tumours, namely the colon tumour which, given the number of cases, gives great importance to this field.

In organizational terms, we usually recommend hepatobiliopancreatic units, where the problem is handled collectively. It is also usual to analyse units with expertise in transplant versus remaining units, according to the specific technical skills of transplantation. Although it becomes difficult to establish the exact number of cases to analyse, this is a field with uniform centralization.

13.2.3 PANCREATIC CANCER

There are 800 new cases of pancreatic cancer every year in Portugal. This field is internationally known for the importance given to the number of surgeries performed in each centre and the post-operative mortality. Usually, the intervals used for defining different behaviour groups are:

i) Less than 10 surgeries a year;
ii) Between 10 and 50 surgeries a year;
iii) 50 or more surgeries a year.

The last group is considered the ideal situation.

However, among the 800 cases diagnosed every year in Portugal, only a minority will have surgery indication, therefore the number of centres will be depending on that number of cases.

13.2.4 RECTAL CANCER

In Portugal, there are approximately 2000 new cases of rectal cancer every year. In this pathology, the importance given to the number of surgeries in each centre is also determinant for the post-operative mortality and local relapse rate.

In the case of colorectal cancer, the ability to use combined modalities of treatment, using chemoradiotherapy and surgery, is determinant, therefore the ability to programme simultaneously these therapies is a critical factor for the treatment's success.

Besides the oncological results, the amount of surgeries performed proved to be determinant in the percentage of patients submitted to sphincter-preserving surgery. We stress out that the relationship between the post-operative mortality and the number of surgeries performed in each centre was decisive in Portugal, namely in high-risk patients.

13.2.5 OESOPHAGEAL CANCER

As for oesophageal cancer, there are around 600 new cases every year in Portugal. Likewise in these tumours, the importance of surgical technique, amount of cases and ability to properly connect different therapy modalities, is essential for success, therefore the existence of clinics dedicated to handle premalignant lesions (Barrett's oesophagus), the ability of early intervention, as well as the existence of solid expertise in transitional lesions pathology, are fundamental for the proper therapy.

13.2.6 STOMACH CANCER

There are around 2900 new cases of stomach cancer in Portugal every year. From the surgical point of view, the same problems observed in oesophageal cancer are applicable to stomach cancer, particularly in cardioesophageal junction tumours. In Portugal, stomach tumours are a particular problem due to the significant incidence rate, probably associated with eating habits and high rate of *Helicobacter Pylori* infection.

The difference between post-operative mortality and resectability rates was associated with the surgery's volume, whereas a recent European multicentric study point out a cut off between 10 and 20 surgeries a year. The accuracy of surgical intervention, namely the lymph node dissection, is strictly related to the surgeon's individual expertise.

13.2.7 BREAST CANCER

In Portugal, there are approximately 5500 new cases of breast cancer every year. At European level, the European society of breast cancer specialists (EUSOMA) established the minimum requirements for creating a breast disease unit. The first requirement is the minimum number of cases treated per year, which was established in 150. This number only depended on assistance quality criteria. Besides the quantity requirements, they further established minimum requirements in terms of organization and

allocated human and technical means, in order to ensure a European uniformity in treating these patients.

These numbers were reassessed by Pagano and assistants, including economic parameters, and these authors conclude that the necessary number of new cases for making a breast unit profitable was 200.

Thus, we may consider 150 to 200 new cases of breast cancer the minimum number for a centre to operate.

Besides casuistics, these units need to guarantee the sentinel lymph node surgery and the possibility of breast reconstruction, as well as the multidisciplinary treatment and dedicated teams.

13.2.8 MELANOMA

In Portugal, there are approximately 800 new cases of melanoma per year.

When planning the units for treating melanoma, it is important to cover the most comprehensive concept of treating pigmented skin lesions, after considering the diagnosis phases and the very different approach among thin lesions and without invading deep-planes and high-risk lesions.
In melanomas, above centralizing the treatment of all patients, it is important to create anchor units, with capacity for reviewing the necessary cases and ensuring the treatment of the most difficult cases, particularly high-risk cases.

The appropriate use of sentinel lymph node technique, although not yet with proven advantages in overall survival documented in controlled studies, enables to apply the lymphadenectomy technique to selected cases, with the subsequent decrease of morbidity.

The pathological criteria used for the proper diagnosis and staging, including the methodology for analysing the sentinel lymph node, also depend on the technical skills and expertise of the surgeon.

At last, the emergence of new drugs, particularly expensive and highly toxic, also limits the centralization of these cases.

13.2.9 CHILDHOOD CANCERS

In Portugal the paediatric oncology is already centralized and its activity is restricted to four centres: Instituto Português de Oncologia (IPO) de Lisboa, E.P.E., Hospital Pediátrico de Coimbra [paediatric hospital]; IPO Porto, E.P.E; and Hospital de São João, E.P.E..

Portugal has a diversified model that ranges from the procedures in specialist hospitals (IPO - Lisbon and Oporto) to the large general hospital (Hospital de São João, E.P.E.) to the paediatric hospital.

Each one of these different models has its advantages and inconveniences, and they are common in countries of reference.

The very notion of paediatric oncology has been suffering changes at international level, with the extension of the reference age and, in recent years, the empowerment of teenage and young adult units. The extension of the paediatric age had the obvious advantage of treating teenagers with therapeutic protocols best suited for them, and which allow better results, and maintaining an environment that is more appropriate to the current way teenagers regard themselves and are regarded.

This paradigm shift also brought new problems to paediatric oncology, which include both new pathologies (very rare or non-existent in the younger children) and new needs of this age group. Therefore it were constructed intermediate and specific units, dedicated to treating teenagers and young adults, usually within paediatric oncology departments in cooperation with adult units.
If we take a look at the Portuguese population up to the age of eighteen there are approximately 300 new cases of cancer per year.

Usually there are identified some specific needs in the paediatric oncology units:

i) An own cancer registry, for the importance of exhaustive knowledge of the cases, treatments and outcomes, due to the rarity of the pathology. In Portugal it is being prepared a national registry of childhood tumours, with the participation of all centres;
ii) The existence of a paediatric environment in all procedures: a dedicated and adjusted area, as well as permanent multidisciplinary teams (e.g. specialist doctors, specialist nurses, dedicated radiologists, specialist pathologist, radiotherapist with expertise in paediatrics);
iii) A clinic dedicated to the survivors which, due to the growing success rate and the increasing expectation of life of this population, is particularly relevant;
iv) The essential psychological support, as well as social support;
v) Dedicated rehabilitation;
vi) School integration.

It has occurred in some countries the centralization of this activity. The most recent and radical example took place in Holland where all paediatric oncology was centralized in Utrecht with the purpose of building one of the three best paediatric oncology centres of the world, with significant decrease in mortality.
In Portugal there is an obvious need of reducing the dispersion of the surgical treatment of the tumours of the central nervous system. Although many of these cases are operated as true emergencies, the current number of centres treating this kind of pathology, taking into consideration the cases frequency, is surely excessive.

The existence of four centres in the country must be reconsidered due to the number of new cases per year. However, there is no reliable literature to defend a specific workload as the minimum required.

Regardless of the centralization, the adoption of common protocols at national level and the joint entry in international cooperative groups must be stimulated and encouraged, including the provision of means for making this goal possible.

It must also be ensured that all patients under the age of 18 are treated in a paediatric environment and that teenage units are planned within the paediatric oncology services and in connection with the adult services.

Regardless of the number of units, we must evolve towards a more advanced mode of organization with the construction of a formal national group for standardizing procedures and centralizing results.

13.3 HEREDITARY METABOLIC DISEASES

The Hereditary Metabolic Diseases are entities of genetic nature in which the metabolism of a certain compound is altered.

They are caused by a specific enzyme deficiency which affects a certain metabolic pathway, leading to the accumulation of substrates, often toxic, and to the reduced or non-existent production of a biologically important product.

The enzyme deficit is the phenotypical consequence of the existence of mutations in one or several coding genes for the metabolic step concerned.

The hereditary metabolic diseases are rare diseases responsible for a significant morbidity and mortality, especially in the paediatric population. More than 600 inborn errors of metabolism are currently identified. They are also very complex pathologies which demand a high scientific preparation, clinical expertise and a constant availability allowing a continuity of care and safeguarding quality of life for these chronic patients.

The potentially treatable forms of these diseases have greater importance by indicating the urgent beginning of the proper and expensive therapeutics.

As examples of these diseases we have diseases caused by toxic metabolites accumulation, diseases related to protein catabolism, diseases related to energy metabolism and diseases involving complex molecules, in which are included the DLS.

The DLS are genetic diseases, rare and with a complex diagnosis, which demand, in order to treat patients, the supply and dispense of expensive medication. In 2012, there were 161 patients under pharmacological treatment in Portugal for the following pathologies:

i) Pompe's disease;
ii) Fabry's disease;
iii) Gaucher's disease;
iv) Niemann-Pick disease type C;
v) Mucopolysaccharidosis (MPS) I (Hurler/Scheie disease);
vi) MPS II (Hunter's disease);
vii) MPS VI (Maroteaux-Lamy disease).

Following the order no. 2545/2013, of the Secretary of State for Health, from February 7th, in which the creation of a Coordinating Commission of Treatment of Lysosomal Storage Diseases (CCTDLS) is determined, it is established that "For purposes of connection with the CCTDLS, the Regional Health Administrations from the North, Centre and Lisbon and Tagus Valley propose for each one of the regions a hospital specialized in diagnosis and treatment of patients with lysosomal diseases, which operates as a centre of excellence, for the purposes foreseen in this order".
Therefore, and as this report deals with the constitution of CR in Portugal (with eventual integration in RER), the GT proposes updating the concept of Centres of Excellence, for the DLS, for the CR and their integration in CR for congenital metabolic diseases.

13.4 HAEMOPHILIA

Haemophilia is a rare genetic disease which affects blood coagulation due to mutation in the anti-haemophilic factors: Factor VIII (regarding haemophilia A) and Factor IX (regarding haemophilia B).

Haemophilia almost exclusively affects males and is a hereditary disease. The prevalence at birth is 1/5,000 children for haemophilia A and 1/30,000 children for haemophilia B.

It is estimated that there are about 2,400 people with haemophilia A or haemophilia B in Portugal that can enjoy an active life, provided they have appropriate treatment by replacing the deficient clotting factor. In some cases, for instance when there is an antibody which inhibits coagulation (substance that prevents coagulation) it is necessary to use specific medication to replace the concentrates of anti-haemophilic factors, forcing the use of a very different therapeutic treatment.

13.5 INTERVENTION CARDIOLOGY AND HAEMODYNAMICS

The rapid evolution of the techniques of percutaneous cardiology intervention has created new challenges and a progressive need to reformulate and reframe the activities of the several centres. The global relation between the volume of procedures performed by operator and centre and the results obtained has been internationally recognized and published, leading to a careful weighting of the balance between the greater accessibility, provided by the geographical proximity, and the necessary concentration of resources, which can ensure appropriate volumes.
In the case of several interventional techniques this weighting leads to a clear conclusion: the reduced global number of procedures arising from the limited universe of candidates to which it applies, entails the need to confine its performance in CED, where high levels of proficiency can be achieved by the operators and where it can be locally developed strict protocols for selecting candidates.

The need of a careful planning also results from the human resources field in which it must be considered the need of a long mandatory training period of two years minimum after the medical specialization in Cardiology (total of seven years of specialized training), as well as the necessary specialization in nursing.
On the other hand, every year new techniques and devices are introduced as technological innovation, often creating answers for situations not previously considered and extending the scope of the target population.

These innovative solutions are generally characterized by:

i) The need for defining and consolidating their real value within the range of available solutions;
ii) Imposing demanding and prolonged learning curves;

iii) Involving very high costs.

These characteristics imply the need for conditioning their use to a careful planning, avoiding an indiscriminate use motivated by the inevitable marketing pressure and by the understandable generalized desire for all innovation.

In a general way, there are in Portugal enough centres of intervention cardiology (and a surplus capacity installed in Lisbon and Coimbra, already partially corrected), therefore it must be strongly discouraged the installation of new centres that will only contribute for a waste of resources and difficulty in planning. In the following years the emphasis should be on consolidating the functioning of the already existent centres, giving them human resources and materials appropriate to the planned activity.

The current intervention cardiology techniques can be divided by using the following systematization:

i) Elective and urgent percutaneous coronary angioplasty techniques;
ii) Interventional percutaneous valvular techniques;
iii) Interventional percutaneous techniques in congenital cardiopathies;
iv) Other techniques of non-coronary intervention, including the so called structural intervention.

Percutaneous coronary angioplasty is the technique with greater diffusion and largest number of procedures at national level. The accessibility in this case should be exclusively determined by the geographical coverage needed to ensure the performance of a coronary angioplasty for reperfusion therapy in the acute myocardial infarction (primary angioplasty).

The techniques for complex coronary angioplasty shall be limited to the centres of high differentiation which shall take into consideration the following (cumulative) mandatory criteria:

i) Annual performance of at least 2,500 diagnostic procedures;
ii) Annual performance of at least 800 coronary angioplasty procedures;
iii) Location at Hospital with Cardiac Surgery;
iv) Recognized training capacity for the subspecialty of Intervention Cardiology.

The performance of interventional percutaneous valvular techniques, including valvulotomies, repair surgeries or implantation of percutaneous valvular prosthesis, and percutaneous treatment of congenital cardiopathies must be limited to centres with these characteristics. It must also be confined to these centres the performance of emerging techniques in the initial year after their introduction. It is also important to promote an analysis integrated with the specialties related to these group of procedures, specially the cardiothoracic surgery.

14 RECOMMENDATIONS

In view of what has been said throughout this document, the GT proposes the following recommendations:

1. **A legal framework for guiding the reference centres shall be established.**

The transposition of the Directive into the national legislation entails, given the inexistence of a legal framework supporting and officially recognizing the CR to be constituted in our country, the development of the pieces of legislation and regulation which establish the general and specific models for creating CR.

This legal and regulatory framework shall establish the following aspects:

i) The definition of the figures of CR, CNA and CA, identifying the model of integration in the Portuguese hospital network and in the RER;
ii) The definition of the general and specific criteria for identifying and officially recognizing the CR in Portuguese territory. These criteria shall be in accordance with those determined by the European Commission, with the aim of a future integration of the national CR in the RER;
iii) The identification of the specific entity of the Ministry of Health responsible for officially recognizing the CR;
iv) The definition of the formal creation process of the CD, GP and CT, intrinsic to the effectiveness of the recognition process of the CR at national level, approving their competencies and defining the head office where they are going to operate;
v) The definition of the official recognition model of the national CR;
vi) The definition and description of the financing model of the priority areas of intervention, pathologies and procedures in the creation of the CR;
vii) The description of the review process of the recognition of the CR;
viii) The need to review all previously regulated situations which gather statutes close to the CR (namely CED, CT and Centres of Excellence), in order to standardize procedures and methodologies, adapting them to the Directive and taking into consideration the recommendation of the European Commission;

ix) The guiding of the National Programme for Rare Diseases and of the National Network of Reference Centres for Rare Diseases in view of the national criteria and conditions, adapting them to the future CR.

2. The priority areas for creating CR in Portugal, which will be developed in 2014, shall be considered.

For the previously stated reasons, the following are considered as priority areas for creating CR:

i) Transplantation of solid organs;
ii) Cancer;
iii) Hereditary Metabolic Diseases;
iv) Haemophilia;
v) Intervention Cardiology and Haemodynamics.

3. A specific financing model shall be taken for the CR and CA, suitable for the purposes of their creation.

The financing modalities and contracts of care to be considered within the scope of the creation of the CR shall comply with the principle that only deserves remuneration by areas/procedures/selected pathologies those entities which are deemed as CR/CA for that purpose. The CR which will be created, as well as the CA of those CR, are responsible for providing a clear and unequivocally defined services portfolio.

4. **The model of integration of the CR in the Portuguese hospital network shall be defined.**

The model of CR and CA shall be duly integrated in the current Portuguese hospital network and in the existing and future RRH, which implies an integrated version of the latter.

5. **A transaction period shall be ensured so that the already existing centres in the first stage can adapt to the new legal framework guiding the CR and CA.**

The group of the first CR shall have ensured a transaction period because, unlikely the candidates for the following stages, they will not have a period of time to adapt.

6. **The public, private and social sectors shall be considered as potential candidates for the statute of CR and CA.**

The creation of CR and CA shall not be exclusive of the public sector. Equal opportunities shall be granted to the private and social sectors, whenever justified and in accordance with a specific development and financing model to be defined.

7. **The recognition process of national CR and respective CA shall be immediately started.**

The process now proposed is by its own nature a somewhat slow process. Such fact entails that the process shall start the earliest possible.

8. **DGS and ACSS shall develop their internal competencies, as well as their own organizational model in order to fully and effectively answer to the creation and development process of the CR in Portugal.**

The process now proposed to be created and developed will be all the more effective if the structures created to respond to this new challenge of the SNS are agile and have less bureaucracy. It is therefore important that both structures jointly create as soon as possible the necessary structures for ensuring the development of this process.

9. **The CR and CA shall be subject to periodic assessment and audit processes.**

It shall be promoted periodic assessment and audit processes performed by national and international independent experts to all CR and CA.

10. **The high differentiation centres and treatment centres, as well as the National Programme of Rare Diseases, shall be clarified and integrated in the concept of CR and CA.**

Over the past years it was created a number of centres with the purpose of approaching a set of particular pathologies and which shall now be reformulated in accordance with the new concepts. Such fact is also applied to the development of the National Programme for Rare Diseases which shall equally take into account the principles now stated.

15 GLOSSARY

In this chapter we present the definition of concepts. Some, although not yet definitely stabilised in accordance with the European dynamic, represent the current state of the art.

Assessment

Assessment is the process carried out by the European Commission, in order to verify the fulfilment of the criteria and conditions demanded to the RER and CR that intend to become or remain full members of a RER (Meeting of the Expert Group of the European Commission for the RER).

Affiliated Centre

An Affiliated Centre is a Portuguese centre which does not comply with the conditions and criteria in order to be officially recognized as national CR but has knowledge and expertise on a certain specific area of competencies recognized by the Ministry of Health. This Centre, on the basis of its services portfolio, shall be connected with a CR of the same specialization area (Work Group).

National Associated Centre

A National Associated Centre is a national CR which the European Commission does not recognize as full member of a RER but with whom it can cooperate (Meeting of the Expert Group of the European Commission for the RER).

Coordinator of the European Reference Network

The Coordinator of a European Reference Network is the professional designated by the members chairing the meetings of the Council of the European Reference Network and which represents that network (Meeting of the Expert Group of the European Commission for the RER).

Council of the European Reference Network

The Council of the European Reference Network is the governance body of each one of the RER, in which all CR participating as full members in that Network are represented (Meeting of the Expert Group of the European Commission for the RER).

Complexity of a Disease or Condition

The complexity of a disease is defined as a combination of factors, symptoms or signs of a certain disease or disorder, which requires a multidisciplinary approach and a well-planned organization over time, because it entails: (i) a high number of possible diagnosis or management options for comorbidity; (ii) a difficult interpretation of the data relating to the clinical and diagnostic tests and (iii) a high risk of complications, morbidity or mortality, related either to the problem, the diagnosis process or the disease management (Meeting of the Expert Group of the European Commission for the RER).

Healthcare

It is understood as healthcare the services care by health professionals to the patients in order to assess, maintain and rehabilitate their health condition, including actions as prescribing, dispensing and providing medication and medical devices (Directive 2011/24/EU of the European Parliament and of the Council, 2011).

Highly Specialized Healthcare

It is understood as Highly Specialized Healthcare those care which present limited casuistics, involving, at least, one of the following factors: (i) high complexity of a given pathology or condition in terms of diagnosis, treatment or management and (ii) high costs of treatment and/or resources (Meeting of the Expert Group of the European Commission for the RER).

Cross-border Healthcare

It is understood as cross-border healthcare those care provided or prescribed in a different Member State from the Member State of affiliation of the patient (Directive 2011/24/EU of the European Parliament and of the Council, 2011)

Designation

It is understood as Designation the generic and structured process after which the European Commission will decide whether the healthcare providers and the RER comply or not with the criteria and conditions stipulated in their Implementation Decision (Meeting of the Expert Group of the European Commission for the RER).

Rare Disease

It is understood as Rare Disease a disease which presents a prevalence not higher than 5 cases per 10,000 inhabitants (Directive 2011/24/EU of the European Parliament and of the Council, 2011).

Multidisciplinary Care Team

It is understood as Multidisciplinary Care Team a group of health professionals from several care areas which by combining different competencies and resources ensure the coordination of healthcare to be provided to the patient (Meeting of the Expert Group of the European Commission for the RER).

Member State of Affiliation

It is understood as Member State of Affiliation the state which is responsible for ensuring previous authorization to the patient for receiving treatment outside his/her Member State of residence (Directive 2011/24/EU of the European Parliament and of the Council, 2011).

Member State of Treatment

It is understood as Member State of Treatment the state where the healthcare are actually provided to the patient. In the case of telemedicine the healthcare are provided in the Member State where the healthcare provider is established (Directive 2011/24/EU of the European Parliament and of the Council, 2011).

Clinical Recommendations or Recommendations on Good Practices

The clinical recommendations are norms based on the scientific evidence of strict and systematic studies of published medical literature, with the purpose of helping the decision-making of health professionals, regarding appropriate care for certain clinical circumstances (Meeting of the Expert Group of the European Commission for the RER).

Incidence

The Incidence consists in the number of new cases of a disease, symptom, death or lesion, which are developed during a specific time period (e.g. year). The incidence shows the probability of a person in that population to be affected by the disease (Bonita, Beaglehole, Kjellstrom, 2006).

Logo

The Logo is the unique graphic identifier that can be used by RER and CR which are full members of a RER, granted by the European Commission and destined to identify them. (Meeting of the Expert Group of the European Commission for the RER).

Prevalence

Prevalence corresponds to a number of cases of a disease which is present in a given population, at a given time (Bonita, Beaglehole, Kjellstrom, 2006).

Reassessment

It is understood by Reassessment the periodic assessment process, subsequent to the designation of a CR, for determining whether a CR and/or RER continue or not to comply with the criteria and conditions of the implementation of the European Reference Networks, stipulated by the European Commission (Meeting of the Expert Group of the European Commission for the RER).

Hospital Reference Network

A Hospital Reference Network is defined as a system through which it is intended to regulate the relationships of complementarity and technical support between all hospital institutions, in order to ensure the access of all patients to the services and units providing healthcare, supported on an integrated system of inter-institutional information. A Hospital Reference Network is expressed by a set of medical specialities and technologies which support several local health systems, allowing: (i) the networking, variable according to the characteristics of the available resources, between regional and national determinants and conditions and the type of speciality in question; (ii) to maximize complementarities in order to take advantage of synergies, concentrating expertise and allowing the development of the knowledge and the specialization of technicians with the consequent improvement of the quality of the care provided; (iii) to concentrate resources allowing to maximize its profitability (Saúde XXXI, 2000).

Representatives of the Reference Centres

The Representatives of the CR are the health professionals, designated from among the member of each one of the CR which are full members of a RER, which represent it in the Council and within the RER, as well coordinate the activities of the CR related to the RER (Meeting of the Expert Group of the European Commission for the RER).

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ATTACHMENTS

Attachment 1. High Differentiation Centres and Treatment Centres in Portugal.

Table A 1. Multiple Sclerosis Treatment Centres

MULTIPLE SCLEROSIS TREATMENT CENTRES	
HEALTH REGION	TREATMENT CENTRE
North	Centro Hospitalar de São João, E.P.E
	Centro Hospitalar de Vila Nova de Gaia/Espinho, E.P.E
	Centro Hospitalar do Alto Ave, E.P.E
	Centro Hospitalar do Porto, E.P.E
	Centro Hospitalar de Vila Real/Peso Régua, E.P.E
	Hospital de Braga
Centre	Centro Hospitalar e Universitário de Coimbra, E.P.E
	Centro Hospitalar de Leiria/Pombal, E.P.E
Lisbon and Tagus Valley	Centro Hospitalar de Setúbal, E.P.E
	Centro Hospitalar de Lisboa Central, E.P.E
	Centro Hospitalar de Lisboa Norte, E.P.E
	Hospital Prof. Doutor Fernando da Fonseca, E.P.E
	Centro Hospitalar de Lisboa Ocidental, E.P.E
Alentejo	Hospital do Espírito Santo Évora, E.P.E
Algarve	Centro Hospitalar do Algarve, E.P.E

Source: Adapted from DGS, Orientation no. 013/2011 from 09/05/2011.

Table A 2. Obesity Treatment Centres

OBESITY TREATMENT CENTRES		
HEALTH REGION	PUBLIC TREATMENT CENTRES	PRIVATE TREATMENT CENTRES
North	Centro Hospitalar do Porto, E.P.E.	Hospital da Prelada, Dr. Domingos Braga da Cruz
	Centro Hospitalar do Alto Ave, E.P.E.	Clipóvoa - Hospital Privado
	Centro Hospitalar de Entre o Douro e Vouga, E.P.E.	Hospital da Arrábida - Gaia, S.A.
	Centro Hospitalar de São João, E.P.E	Instituto CUF - Diagnóstico e Tratamento, S.A.
	Centro Hospitalar de Vila Nova de Gaia / Espinho, E.P.E.	Hospitais Privados de Portugal - HPP Norte, S.A.
	Hospital de Braga	Hospital da Trofa, S.A.
		Celestial Ordem Terceira da Santíssima Trindade
		Casa de Saúde de Guimarães, S.A.
		Santa Casa da Misericórdia de Riba d'Ave - Hospital Narciso Ferreira
		Venerável Ordem Terceira de Nossa Senhora do Carmo
Centre	Hospital Distrital da Figueira da Foz, E.P.E.	Círia - Hospital Privado de Aveiro, S.A.
	Centro Hospitalar de Coimbra, E.P.E.	Intercir - Centro Cirúrgico de Coimbra, S.A.
	Hospitais da Universidade de Coimbra, E.P.E.	Casa de Saúde de Santa Filomena, SA
	Unidade Local de Saúde da Guarda, E.P.E.	
	Centro Hospitalar de Leiria-Pombal, E.P.E	
Lisbon and Tagus Valley	Centro Hospitalar de Setúbal, E.P.E.	Hospital CUF Infante Santo, S. A.
	Centro Hospitalar do Médio Tejo, E.P.E.	Clisa, Clínica de Santo António, S.A.
	Centro Hospitalar de Lisboa Norte, E.P.E.	British Hospital Lisbon XXI, S.A.
	Centro Hospitalar de Lisboa Ocidental, E.P.E	Lasercenter/Citro
	Centro Hospitalar de Lisboa Central, E.P.E	Hospital de Santiago
	Hospital Distrital de Santarém, E.P.E.	Hospital dos Lusíadas
	Hospital Prof. Doutor Fernando da Fonseca, E.P.E.	SAMS - Hospital
		Hospital da Luz
		Hospital Cuf Descobertas
		Barroclínica
Alentejo	Hospital do Espírito Santo, E.P.E.	
Algarve	Centro Hospitalar do Algarve, E.P.E.	Hospital Privado Santa Maria de Faro
		Hospital Particular do Algarve, S.A.

Source: Adapted from DGS, Normative Memorandum no. 18/DSCS/DGID from 11/08/2008.

Table A 3. High Differentiation Centre for obesity

HIGH DIFFERENTIATION CENTRES FOR OBESITY	
HEALTH REGION	HIGH DIFFERENTIATION CENTRES
North	Centro Hospitalar de São João, E.P.E

Source: Adapted from DGS, Normative Memorandum no. 19/DSCS/DGID from 12/08/2008.

Table A 4. Treatment Centres for vascular accesses for haemodialysis

TREATMENT CENTRES FOR VASCULAR ACCESSES FOR HAEMODIALYSIS		
HEALTH REGION	PUBLIC TREATMENT CENTRES	PRIVATE TREATMENT CENTRES
North		Instituto CUF - Diagnóstico e Tratamento, S.A. - Centro de Tratamento para Acessos Vasculares para Hemodiálise
		GEV Grupo de Estudos Vasculares Lda
		BONFIMED - Clínica de Diagnóstico do Bonfim, Unipessoal, Lda.
		Caledial, Centro de Hemodiálise de Gaia, SA
Centre	Centro Hospitalar de Coimbra, E.P.E.	SANFIL - Casa de Saúde de Santa Filomena, S.A.
		NephroCare Portugal / CAV-Centro de Acessos Vasculares Coimbra
Lisbon and Tagus Valley	Centro Hospitalar de Setúbal, E.P.E.	Nephrocare Portugal - CAV Centro de Acesso Vasculares Lisboa
	Hospital Garcia de Orta, E.P.E.	Diaverum, Investimentos e Serviços, Unidade de Entrecampos
	Centro Hospitalar Lisboa Central, E.P.E.	Clínica Europa - Serviços Médicos, S.A.
	Centro Hospitalar Lisboa Norte E.P.E.	Pluribus Diálise – Benfica, S.A
	Centro Hospitalar de Lisboa Ocidental, E.P.E.	
	Centro Hospitalar Médio Tejo, E.P.E.	
Alentejo	Hospital do Espírito Santo de Évora, E.P.E.	
Algarve		HPP - Hospital de São Gonçalo de Lagos

Source: Adapted from DGS, Orientation no. 032/2011 from 26/10/2011.

Table A 5. High Differentiation Centres for Nephrology

HIGH DIFFERENTIATION CENTRES FOR NEPHROLOGY	
HEALTH REGION	HIGH DIFFERENTIATION CENTRES
North	Centro Hospitalar de São João, E.P.E.
Centre	Centro Hospitalar e Universitário de Coimbra, E.P.E.

Source: Adapted from DGS, Normative Memorandum no. 14/DSCS/DGID from 31/07/2008.

Table A 6. Treatment Centres for Type 1 Diabetes, through continuous subcutaneous perfusion of insulin

TREATMENT CENTRES FOR TYPE 1 DIABETES – CONTINUOUS SUBCUTANEOUS PERFUSION OF INSULIN		
HEALTH REGION	PUBLIC TREATMENT CENTRES	PRIVATE TREATMENT CENTRES
North	Centro Hospitalar de São João, E.P.E.	
	Centro Hospitalar do Porto, E.P.E.	
	Centro Hospitalar Vila Nova de Gaia/Espinho, E.P.E.	
	Hospital de Braga	
	Hospital Santa Maria Maior, E.P.E.	
	Unidade Local de Saúde de Matosinhos, E.P.E.	
	Unidade Local de Saúde do Alto Minho, E.P.E.	
Centre	Centro Hospitalar e Universitário de Coimbra, E.P.E.	
Lisbon and Tagus Valley	Centro Hospitalar Barreiro/Montijo, E.P.E.	Associação Protetora dos Diabéticos de Portugal
	Hospital Curry Cabral, E.P.E.	
	Centro Hospitalar de Torres Vedras, E.P.E.	
	Centro Hospitalar Lisboa Norte, E.P.E.	
	Centro Hospitalar Lisboa Ocidental, E.P.E.	
	Hospital Garcia de Orta, E.P.E.	

Source: Adapted from DGS, Normative Memorandum no. 17/DSCS/DGID from 04/08/2008.

Attachment 2. Evaluation grid of the proposals to Reference Centres

Table A 7. Evaluation grid of proposals to CR.

AREA	HORIZONTAL CONDITIONS	REQUIREMENTS BY AREA
JOINT RESPONSIBILITY AND PATIENT CENTRED CARE	Providing highly specialized care with high quality, safety and which are patient centred. Ensuring patient's privacy Ensuring to the patients the right to informed consent and information regarding their health/disease condition. Ensuring the clarified joint responsibility of the patients.	1. Description of the area of action to which the centre is applying. 2. Description of the clinical, technical and technological competencies demonstrating differentiated ability of action and connection with the national, European and international counterparts. 3. Demonstration of an organizational circuit for ensuring patient's privacy. 4. Existence of Rules of Procedure regarding the access of the patients to the informed and clear consent and to their clinical information. 5. Number of partnership agreements with civil society entities. 6. Existence of a five-year plan for participating in campaigns of population awareness, in the centre's area of action.
QUALITY, SAFETY AND GOOD PRACTICES	Ensuring the existence of a quality management system that includes a safety programme for the patients. Having process and results indicators. Ensuring a transparency mechanism about results information, treatment options and quality and safety standards in force at the Centre. Ensuring the capacity, knowledge and expertise to diagnose, follow-up and manage the patients with evidence of good results. Actively measuring the patients' experience and ensuring feedback reports. Having capacity to benchmark the quality and safety, as well as to promote the best practices at national and international level. Complying with the rules for personal data protection and accessibility to medical records and clinical information, in accordance with the national legislation and provisions of the European Union regarding this subject.	1. Evidence of an Accreditation certificate or declaration of commitment of immediate enrolment in an accreditation process. 2. Existence of an implementation plan for a quality management system. 3. Publication, on the institutional website, of the results of the notifications performed in the National System of Notification of Incidents and Adverse Events. 4. Stating the quality and process indicators and results. 5. Evidence of annual publication of results on the institutional website. 6. The institutional website must provide the diagnostic and therapeutic options in the centre's area of action. 7. Promotion on the institutional website of the quality and safety norms adopted by the centre. 8. Existence of an annual monitoring system for the patient's experience. 9. Existence of an annual benchmark report, European and/or international, about the quality and safety indicators, in the centre's area of action. 10. Documentary evidence of the authorizations granted by the National Commission of Data Protection. 11. Presentation of the casuistics of the past 5 years, in the centre's area of action. 12. Substantiation of the application's relevance, in the centre's area of action, compared to the European or international state of the art. 13. Existence of an annual monitoring system for the patients' satisfaction. 14. Demonstration of specialized technical consultancy, provided by team elements, in the centre's area of action. 15. Demonstration of having participated in work groups for preparing technical recommendations at national, European and international level.

AREA	HORIZONTAL CONDITIONS	REQUIREMENTS BY AREA
ORGANIZATION AND MANAGEMENT	Ensuring the existence of medical records	1. Description of the existing means for medical records. 2. Evidence of having participated in national clinical data recording, European and/or international, regarding the centre's area of action. 3. Evidence of handling and settling complaints presented in the *Sim-Cidadão* System. 4. Existence of an organogram demonstrating the internal organization of the centre and its external connection at national, European or international level. 5. Existence of formal agreements with other units of resources not exclusively allocated to the centre, which are needed for a proper continuity of care provision. 6. Definition of the centre's aims for the next 5 years. 7. Existence of a plan for ensuring the centre's stability and sustainability for the next 5 years. 8. Identification of the existing weak points and description of the respective improvement plan. 9. No. of elements in the multidisciplinary team which integrate the centre, by specialty and area of action, including their *curricula vitae*. 10. Existence of a mechanism for identifying unfulfilled healthcare needs in the centre's area of action. 11. Evidence of a response plan, for the next 5 years, for the unfulfilled healthcare needs in the centre's area of action. 12. List of indicators negotiated in a programme contract within the scope of the centre's action. 13. Demonstration of cost-effective action of the centre regarding its national, European or international counterparts. 14. Description of the coding systems used, recognized at national and European level. 15. Publication on the institutional website of the fees charged by the centre in its area of action. 16. Assurance that care will be provided to cross-border patients after they have been discharged.
	Ensuring the existence of a complaint system and the access to compensation systems for the patients.	
	Demonstrating evidence of organization and management rules and practices, explicit and transparent, which include procedures related to the management of cross-border patients in its area of knowledge and expertise.	
	Having capacity to provide essential medical care in case of a sudden lack of resources or assurance of reference to alternative resources.	
	Demonstrating capacity to maintain stability, technical ability and expertise of the CR, through a sustainable plan of human resources management and technological update.	
	Having a plan for continuing the activities which ensure the sustainability of the CR with a defined time horizon.	
	Ensuring the use of standardized information and coding systems recognized at national and international level.	
	Ensuring the transparency of the fees charged to national and international patients by the CR	
	Having the ability to perform cross-border communication after the patient's discharge.	
	Demonstrating capacity to cooperate with other CR and with RER, whether at national or international level	

AREA	HORIZONTAL CONDITIONS	REQUIREMENTS BY AREA
RESEARCH AND TRAINING CAPACITY	Demonstrating teaching and training capacity, including distance learning and training, at academic and specialized level, in the area of competence and expertise.	1. Number of awards/scientific references received by the team elements, over the past 5 years. 2. Number of training hours received by the team elements in their area of action, over the past 5 years. 3. Number of times the team elements have participated in academic juries, over the last 5 years. 4. Number of hours spent by the team elements for post-graduate teaching, over the past 5 years. 5. Number of hours spent by the team elements for graduate teaching, over the past 5 years. 6. Number of graduates in specialization oriented by the team elements, over the past 5 years. 7. Number of master's students oriented by the team elements, over the past 5 years. 8. Number of PhD students oriented by the team elements, over the past 5 years. 9. Number of team elements holding a PhD. 10. Number of team elements which are researchers but do not have a PhD. 11. Number of research projects funded or which have applied for funding, over the past 5 years, subscribed by one or more team elements. 12. Number of scientific articles published in indexed journals over the past 5 years, having one or more team elements as author. 13. Number of partnership agreements with national, European and/or international research centres.
	Having the research capacity in the area of expertise.	
	Demonstrating proven expertise in collaborative research and participation in European or international research networks.	
INFORMATION SYSTEMS	Demonstrating capacity to make the mobility of national and international expertise easier, physically or virtually, through an information system and e-health tools, namely through telemedicine.	1. Identification of the existing information systems. 2. Identification of the e-health tools used. 3. Demonstration of having participated in epidemiological surveillance studies per year, over the past 5 years.
	Demonstrating the use of the best technologies and best treatments, in its area of competence and expertise, based on knowledge and evidence.	

Attachment 3. Prevalence of rare diseases according to *Orphanet*.

Table A 8. List of the prevalence of rare diseases according to *Orphanet*.

ORPHA Number	Disease or group of diseases	Estimated prevalence (/100,000)
48	Congenital bilateral aplasia of the vas deferens	50
823	Isolated spina bifida	50
535	Cutaneous lupus erythematosus	50
71529	Obesity due to melanocortin 4 receptor deficiency	50
706	Patent arterial duct	50
157798	Hyperplastic polyposis syndrome	50
648	Noonan syndrome	50
67037	Squamous cell carcinoma of head and neck	49
209893	Congenital isolated thyroxine-binding globulin deficiency	46
247	Arrhythmogenic right ventricular dysplasia	43.5
45360	Ménière disease	42.5
3375	Trisomy X	42.5
801	Scleroderma	42
217071	Renal cell carcinoma	< 42
1646	Chromosome Y deletion	40
294	Foetal cytomegalovirus syndrome	40
101016	Romano-Ward long QT syndrome	40
768	Familial long QT syndrome	40**
98715	Uveitis	38
226295	Primary hypothyroidism	37.5
209989	Non-papillary transitional cell carcinoma of the bladder	37
545	Follicular lymphoma	36
288	Hereditary elliptocytosis	35
2764	Osteochondritis dissecans	35
70475	Radiation proctitis	35
1549	Cryptosporidiosis	34
226292	Permanent congenital hypothyroidism	33.3**
858	Congenital toxoplasmosis syndrome	33
3303	Tetralogy of Fallot	33**
216675	Transposition of the great arteries	32.5
2368	Gastroschisis	31.4
69	Amyloidosis	30
213500	Rare ovarian cancer	30
729	Polycythemia vera	30
791	Retinitis pigmentosa	30
63443	Gastric cancer	< 30
442	Congenital hypothyroidism	29
467	Non-acquired combined pituitary hormone deficiency	29
3189	Pulmonary valve stenosis	28.4**
1656	Dermatitis herpetiformis	27
2140	Congenital diaphragmatic hernia	27**
67038	B-cell chronic lymphocytic leukaemia	27
70568	Posttransplant lymphoproliferative disease	26.2
54057	Thrombotic thrombocytopenic purpura	25.5
701	Alopecia universalis	25
145	Hereditary breast cancer syndrome	25
60	Alpha-1-antitrypsin deficiency	25
2073	Narcolepsy-cataplexy	25
90291	Systemic sclerosis	25
95719	Thyroid hemiagenesis	25
3002	Immune thrombocytopenic purpura	25
93402	Syndactyly type 1	25
94058	Neovascular glaucoma	24.4
1199	Esophageal atresia	24.3
171901	Primary cutaneous T-cell lymphoma	24
557	Isolated anorectal malformation	24
3318	Essential thrombocythemia	24
3394	Soft tissue sarcoma	23.7
228113	Anal fistula	23
90062	Acute liver failure	23
636	Neurofibromatosis type 1	23
2578	MURCS association	22**
166	Charcot-Marie-Tooth disease	22
95711	Congenital hypothyroidism due to developmental anomaly	21.3
70476	Vernal keratoconjunctivitis	21
85410	Oligoarticular juvenile arthritis	20.5
1329	Complete atrioventricular canal	20**
1330	Partial atrioventricular canal	20
35093	Scaphocephaly	20
822	Hereditary spherocytosis	20
657	Congenital isolated hyperinsulinism	20
174590	Congenital hypogonadotropic hypogonadism	20
35122	Congenital sucrase-isomaltase deficiency	20
544	Diffuse large B-cell lymphoma	20
589	Myasthenia gravis	20
130	Brugada syndrome	20
558	Marfan syndrome	20
881	Turner syndrome	20
908	Fragile X syndrome	20
52688	Myelodysplastic syndromes	20

ORPHA Number	Disease or group of diseases	Estimated prevalence (/100,000)
3389	Tuberculosis	20
73267	Hypernychthemeral syndrome	18.5
704	Pemphigus vulgaris	18
69061	Idiopathic steroid-sensitive nephrotic syndrome	18
29073	Multiple myeloma	17.5
154	Familial isolated dilated cardiomyopathy	17.5
85445	Secondary amyloidosis	17
221	Dermatomyositis	17
83313	Boutonneuse fever	17
461	X-linked ichthyosis	16.6
1037	Arthrogryposis multiplex congenita	16.1
1201	Atresia of small intestine	16
36258	Buerger disease	16
774	Hereditary haemorrhagic telangiectasia	16
137599	Stromal keratitis	16
232	Sickle cell anaemia	15
1606	1p36 deletion syndrome	15**
2828	Young adult-onset Parkinsonism	15
163934	Atopic keratoconjunctivitis	15
797	Sarcoidosis	15
2382	Lennox-Gastaut syndrome	15
94093	Neuroleptic malignant syndrome	15
187	Citrullinemia	14.4
388	Hirschsprung disease	14.3**
95712	Thyroid ectopia	14.2
214	Cystinuria	14
186	Primary biliary cirrhosis	13.5
828	Stickler syndrome	13.5
2162	Holoprosencephaly	13.4**
904	Williams syndrome	13.3**
70589	Bronchopulmonary dysplasia	13
44890	Gastrointestinal stromal tumour	13
586	Cystic fibrosis	12.6
903	Von Willebrand disease	12.5
3193	Supravalvular aortic stenosis	12.5
2415	Lymphatic malformation	12.5
285	Ehlers-Danlos syndrome, hypermobility type	12.5
90050	Retinopathy of prematurity	12.2**
217074	Pancreatic carcinoma	12
42	Medium chain acyl-CoA dehydrogenase deficiency	12**
660	Omphalocele	12
415	Hyperornithinemia-hyperammonemiahomocitrullinuria	12
1866	Focal dystonia	11.7
2032	Idiopathic pulmonary fibrosis	11.5
635	Neuroblastoma	11.3
70573	Small cell lung cancer	11.2

ORPHA Number	Disease or group of diseases	Estimated prevalence (/100,000)
171	Primary sclerosing cholangitis	11
890	Hepatic veno-occlusive disease	11
652	Multiple endocrine neoplasia type 1	11
3109	Mayer-Rokitansky-Küster-Hauser syndrome	11
700	Alopecia totalis	10.5
36205	Collagenous colitis	10.5
930	Idiopathic achalasia	10
65	Leber congenital amaurosis	10
31112	Dermatofibrosarcoma protuberans	10
1146	Digitotalar dysmorphism	10
827	Stargardt disease	10
569	Familial hemiplegic migraine	10
717	Catecholamine-producing tumour	10
182067	Glial tumour	10
900	Granulomatosis with polyangiitis	10
418	Congenital adrenal hyperplasia	10
58017	Hairy cell leukaemia	10
98293	Hodgkin lymphoma	10
33475	Meningococcal meningitis	10
603	Welander distal myopathy	10
654	Nephroblastom	10
64740	Recurrent acute pancreatitis	10
35098	Isolated plagiocephaly	10
233	Duane retraction syndrome	10
3260	Idiopathic hypereosinophilic syndrome	10
3286	Catecholaminergic polymorphic ventricular tachycardia	10
68411	Rare bone tumour	10
243	46,XX gonadal dysgenesis	< 10
567	22q11.2 deletion syndrome	9.6**
1203	Duodenal atresia	9
2443	Mitochondrial oxidative phosphorylation disorder due to nuclear DNA anomalies	9
137577	Neonatal brain injury	9
519	Acute myeloid leukaemia	9
98292	Mastocytosis	9
805	Tuberous sclerosis	8.8
3380	Trisomy 18	8.6**
99981	Apnea of prematurity	8.5
3280	Syringomyelia	8.4
644	NARP syndrome	8.3
137914	Choanal atresia	8.2
194	Ocular coloboma	8**
220402	Limited cutaneous systemic sclerosis	8
85408	Juvenile rheumatoid factor-negative polyarthritis	8
90290	CREST syndrome	8
412	Hyperlipoproteinemia type 3	7.8
448	Haemophilia	7.7

ORPHA Number	Disease or group of diseases	Estimated prevalence (/100,000)
478	Kallmann syndrome	7.7
2004	Laryngo-tracheo-esophageal cleft	7.5**
1172	Autosomal recessive cerebellar ataxia	7
1332	Medullary thyroid carcinoma	7
212	Cystathioninuria	7
399	Huntington disease	7
98878	Haemophilia A	7
666	Osteogenesis imperfecta	7
2059	Fryns syndrome	7**
821	Sotos syndrome	7**
3366	Trigonocephaly	6.7
42062	Iminoglycinuria	6.68
50839	Cat-scratch disease	6.6
57145	SUNCT syndrome	6.6
732	Polymyositis	6.5
553	Cushing syndrome	6.5
52759	Vasculitis	6.3
609	Tibial muscular dystrophy	6
905	Wilson disease	6
716	Phenylketonuria	6
46724	Cerebral arteriovenous malformation	6
521	Chronic myeloid leukaemia	6
683	Progressive supranuclear palsy	6
733	Familial adenomatous polyposis	6
55	Oculocutaneous albinism	5.9
85438	Enthesitis-related arthritis	5.7
30391	Biliary atresia	5.6
705	Pendred syndrome	5.5**
2440	Split hand-split foot malformation	5.4**
2542	Isolated anophthalmia - microphthalmia	5.3
819	Smith-Magenis syndrome	5.3
1209	Tricuspid atresia	5.2**
803	Amyotrophic lateral sclerosis	5.2
963	Acromegaly	5
85414	Systemic-onset juvenile idiopathic arthritis	5
35099	Brachycephaly	5
55880	Chondrosarcoma	5
63260	Craniorachischisis	5
348	Fructose-1,6-bisphosphatase deficiency	5**
244	Primary ciliary dyskinesia	5
251	Multiple epiphyseal dysplasia	5
97242	Congenital muscular dystrophy	5
98896	Duchenne muscular dystrophy	5
53	Albers-Schönberg osteopetrosis	5
614	Thomsen and Becker disease	5
60015	Parietal foramina	5

ORPHA Number	Disease or group of diseases	Estimated prevalence (/100,000)
2189	Hydrolethalus	5**
89936	X-linked hypophosphatemia	5
469	Fructose intolerance	5
668	Osteosarcoma	5
685	Hereditary spastic paraplegia	5
792	X-linked retinoschisis	5
1306	Buschke-Ollendorff syndrome	5
90309	Ehlers-Danlos syndrome type 1	5
718	Isolated Pierre Robin syndrome	5**
280062	Calciphylaxis	<5
886	Usher syndrome	4.8
88629	Tritanopia	4.8
946	Acrocephalo-syndactyly (generic term)	4.6
102	Multiple system atrophy	4.6
273	Steinert myotonic dystrophy	4.5
85436	Juvenile psoriatic arthritis	4.2
85435	Juvenile rheumatoid factor-positive polyarthritis	4.2
2130	Hemimelia	4.15
1034	Familial Amniotic bands	4**
70482	Oesophageal carcinoma	4
79140	Cutaneous neuroendocrine carcinoma	4
278	Corticobasal degeneration	4
281	5p deletion	4**
95716	Familial thyroid dyshormonogenesis	4
269	Facioscapulohumeral dystrophy	4
117	Behçet disease	4
96253	Cushing disease	4
220393	Diffuse cutaneous systemic sclerosis	4
1572	Common variable immunodeficiency	4
52416	Mantle cell lymphoma	4
101330	Porphyria cutanea tarda	4
915	Aarskog-Scott syndrome	4
2116	Hartnup syndrome	4
778	Rett syndrome	4
301	Ependymal tumour	3.85
1070	Anisakiasis	3.8
98848	Indolent systemic mastocytosis	3.8
97245	Congenital myopathy	3.8
79126	Acute interstitial pneumonia	3.8
809	Sharp syndrome	3.8
2932	Chronic inflammatory demyelinating polyneuropathy	3.7
818	Smith-Lemli-Opitz syndrome	3.7**
3451	West syndrome	3.7**
3465	Worster-Drought syndrome	3.7
3378	Trisomy 13	3.7**
97230	Solar urticaria	3.6

ORPHA Number	Disease or group of diseases	Estimated prevalence (/100,000)
43	X-linked adrenoleukodystrophy	3.5
95713	Athyreosis	3.5
95720	Thyroid hypoplasia	3.5
2655	Thanatophoric dysplasia	3.5**
287	Ehlers-Danlos syndrome, classic type	3.5
36414	Brain stem tumour	3.5
68	Amoebiasis Due to Free-Living Amoebae (facultative parasite)	<3.5
2103	Guillain-Barré syndrome	3.45
104008	Short bowel syndrome	3.4
75377	Central areolar choroidal dystrophy	3.33
49382	Achromatopsia	3.3
429	Hypochondroplasia	3.3
2467	Systemic mastocytosis	3.3
2901	Parsonage-Turner syndrome	3.3
926	Acatalasemia	3.2
1048	Anencephaly	3.2**
50251	Mesothelioma	3.1
767	Polyarteritis nodosa	3.1
98916	Acute inflammatory demyelinating polyradiculoneuropathy	3.1
2322	Kabuki syndrome	3.1
99	Autosomal dominant cerebellar ataxia	3
70	Proximal spinal muscular atrophy	3
136	CADASIL	3
282	Frontotemporal dementia	3
70591	Chronic thromboembolic pulmonary hypertension	3
673	Malaria	3
794	Saethre-Chotzen syndrome	3**
36234	Bacterial toxic-shock syndrome	3
653	Multiple endocrine neoplasia type 2	2.9
374	Goldenhar syndrome	2.8
39812	Graft versus host disease	2.76
506	Leigh syndrome	2.75**
52	Alagille syndrome	2.7**
15	Achondroplasia	2.6**
100070	Progressive non-fluent aphasia	2.5
983	XY Gonadal agenesis	2.5
94	Astrocytoma	2.5
1872	Cone rod dystrophy	2.5
97927	Peripheral resistance to thyroid hormones	2.5
75249	Familial isolated restrictive cardiomyopathy	2.5
703	Bullous pemphigoid	2.5
758	Pseudoxanthoma elasticum	2.5
2337	Non-epidermolytic palmoplantar keratoderma	2.5
116	Beckwith-Wiedemann syndrome	2.5**
358	Gitelman syndrome	2.5
70588	Meconium aspiration syndrome	2.44

ORPHA Number	Disease or group of diseases	Estimated prevalence (/100,000)
304	Epidermolysis bullosa simplex	2.4
2023	Malignant fibrous histiocytoma	2.4
3440	Waardenburg syndrome	2.4
319	Ewing sarcoma	2.33
6	3-methylcrotonylglycinuria	2.3**
3095	Atypical Rett syndrome	2.22
2869	Peutz-Jeghers syndrome	2.2**
231178	Usher syndrome type 2	2.2
33276	Kaposi's sarcoma	2.11
70567	Cholangiocarcinoma	2.1
217	Isolated Dandy-Walker malformation	2.1**
1848	Bilateral renal agenesis	2**
3346	Tracheal agenesis	2**
2911	Poland syndrome	2**
95	Friedreich ataxia	2
54595	Craniopharyngioma	2
280	4P deletion	2**
190	Coats' disease	2
207	Crouzon disease	2
218	Darier disease	2
168782	Childhood disintegrative disorder	2
1699	Trisomy 12p	2**
321	Multiple osteochondromas	2
352	Galactosemia	2**
157835	Paroxysmal hemicrania	2
93323	Fibular hemimelia	2
98879	Haemophilia B	2
389	Langerhans cell histiocytosis	2
98841	Anaplastic large cell lymphoma	2
385	Neurodegeneration with brain iron accumulation	2
626	Large congenital melanocytic nevus	2
2369	Limb body wall complex	2**
3129	Sarcosinemia	2
63	Alport syndrome	2
480	Kearns-Sayre syndrome	2
2345	Isolated Klippel-Feil syndrome	2
185	Scimitar syndrome	2**
861	Treacher-Collins syndrome	2
53693	GRACILE syndrome	2**
2614	Nail-patella syndrome	2
909	Cerebrotendinous xanthomatosis	2
2017	Sternal cleft	<2
27	Vitamin B12-unresponsive methylmalonic acidemia	1.9
10	48,XXYY syndrome	1.9**
199	Cornelia de Lange syndrome	1.9
377	Gorlin syndrome	1.8

ORPHA Number	Disease or group of diseases	Estimated prevalence (/100,000)
53271	Muenke syndrome	1.8**
481	Kennedy disease	1.7**
2182	X-linked hydrocephalus	1.7
470	Lysinuric protein intolerance	1.7**
637	Neurofibromatosis type 2	1.7
888	Van der Woude syndrome	1.7
5	Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency	<1.7
394	Classical homocystinuria	1.65
899	Walker-Warburg syndrome	1.65**
64747	X-linked Charcot-Marie-Tooth disease	1.6
750	Pseudoachondroplasia	1.6
1915	Foetal alcohol syndrome	1.6**
739	Prader-Willi syndrome	1.6
98755	Spinocerebellar ataxia type 1	1.5
98756	Spinocerebellar ataxia type 2	1.5
98757	Spinocerebellar ataxia type 3	1.5
104	Leber hereditary optic neuropathy	1.5
180	Choroideremia	1.5
71211	Devic disease	1.5
35689	Primary lateral sclerosis	1.5
799	Schizencephaly	1.5**
365	Glycogen type 2	1.5
182090	Pulmonary arterial hypertension	1.5
422	Primary pulmonary hypertension	1.5
549	Legionellosis	1.5
168811	Malignant peritoneal mesothelioma	1.5
641	Multifocal motor neuropathy with conduction block	1.5
95161	Chronic hepatic porphyria	1.5
81	Antisynthetase syndrome	1.5
137	Congenital disorder of glycosylation	1.5**
131	Budd-Chiari syndrome	1.5
192	Coffin-Lowry syndrome	1.5
231169	Usher syndrome type 1	1.5
2019	Femur-fibula-ulna complex	1.5
168956	Hypereosinophilic syndrome	1.5
284400	Small cell carcinoma of the bladder	<1.5
83418	Proximal spinal muscular atrophy type 2	1.42
664	Ornithine transcarbamylase deficiency	1.4**
250923	Isolated aniridia	1.38
49041	Retroperitoneal fibrosis	1.38
195	Cat-eye syndrome	1.35
168491	Late infantile neuronal ceroid lipofuscinosis	1.3
564	Meckel syndrome	1.3**
1880	Ebstein malformation	1.25
83330	Proximal spinal muscular atrophy type 1	1.25

ORPHA Number	Disease or group of diseases	Estimated prevalence (/100,000)
829	Adult Still's disease	1.25
2209	Maternal hyperphenylalaninemia	1.25
2481	Neurocutaneous melanocytosis	1.25
87	Apert syndrome	1.25
731	Autosomal recessive polycystic kidney disease	1.2
628	Diastrophic dwarfism	1.2
46485	Superficial pemphigus	1.2
2750	Orofaciodigital syndrome type 1	1.2**
97231	Ligneous conjunctivitis	1.1
892	Von Hippel-Lindau disease	1.1
72	Angelman syndrome	1.1
140874	Joubert syndrome and related disorders	1.1**
790	Retinoblastoma	1.05
1557	Cutis verticis gyrata - intellectual disability	1.02
33	Isovaleric acidemia	1
85	Congenital dyserythropoietic anemia	1
91378	Hereditary angioedema	1
100	Ataxia-telangiectasia	1
1177	Harding ataxia	1
267	Calpainopathy	1
1501	Adrenocortical carcinoma	1
88673	Hepatocellular carcinoma	1
177	Rhizomelic chondrodysplasia punctata	1
25	Glutaryl-CoA dehydrogenase deficiency	1**
94068	Spondyloepiphyseal dysplasia congenita	1**
254	Spondylometaphyseal dysplasia	1
98969	Macular corneal dystrophy	1
34515	Autosomal recessive limb-girdle muscular dystrophy type 2I	1
270	Oculopharyngeal muscular dystrophy	1
183	Chung-Strauss disease	1
355	Gaucher disease	1
487	Krabbe disease	1**
646	Niemann-Pick disease type C	1
296	Enchondromatosis	1
360	Glioblastoma	1
95715	Congenital hypothyroidism due to transplacental passage of maternal TSH-binding inhibitory antibodies	1
86872	T-cell large granular lymphocyte leukaemia	1
531	Lissencephaly type 1, due to LIS 1 anomalies	1**
51577	Lissencephaly Type 2	1**
824	Myelofibrosis with myeloid metaplasia	1
606	Proximal myotonic myopathy	1
607	Nemaline myopathy	1
579	Mucopolysaccharidosis type 1	1**
681	Hypokalaemia periodic paralysis	1

ORPHA Number	Disease or group of diseases	Estimated prevalence (/100,000)
67043	Acanthamoeba keratitis	1
50	Aicardi syndrome	1**
189	Clouston syndrome	1
286	Ehlers-Danlos syndrome, type 4	1
1900	Ehlers-Danlos syndrome, type 6	1**
475	Joubert syndrome	1
710	Pfeiffer syndrome	1
2134	Atypical haemolytic uremic syndrome	1
43393	Lambert-Eaton myasthenic syndrome	1
647	Nijmegen breakage syndrome	1**
396	Chronic hiccup	1
1552	Currarino triad	1
180242	Malignant tumour of fallopian tubes	1
945	Acalvaria	<1**
441	Pure autonomic failure	<1
90970	Primary lipodystrophy	<1
77259	Gaucher disease type 1	0.94
2131	Alternating hemiplegia	0.9**
79278	Erythropoietic protoporphyria	0.9
48162	Lewis-Sumner syndrome	0.9
783	Rubinstein-Taybi syndrome	0.9**
551	MERRF syndrome	0.9
581	Mucopolysaccharidosis type 3	0.87**
54	X-linked recessive ocular albinism	0.8
263	Limb-girdle muscular dystrophy (generic term)	0.8
79361	Inherited epidermolysis bullosa	0.8
169793	Severe haemophilia B	0.8
3169	Sirenomelia	0.8**
3312	Thalidomide embryopathy	0.77**
610	Bethlem myopathy	0.77
2137	Chronic autoimmune hepatitis	0.75
66646	Cutaneous mastocytosis	0.75
667	Malignant osteopetrosis	0.75**
726	Alpers syndrome	0.7**
110	Bardet-Biedl syndrome	0.7
752	17-beta-hydroxysteroid dehydrogenase deficiency	0.68
124	Blackfan-Diamond anemia	0.67**
79318	CDG type 1A syndrome	0.64**
93284	Spondyloepiphyseal dysplasia tarda	<0.6
79168	Disorder of bile acid synthesis	0.6
169799	Mild haemophilia B	0.6
169796	Moderately severe haemophilia B	0.6
580	Mucopolysaccharidosis type 2	0.6**
240103	Progressive supranuclear palsy - corticobasal syndrome	<0.6
93473	Hurler syndrome	0.57
3463	Wolfram syndrome	0.57
538	Lymphangioleiomyomatosis	0.56

ORPHA Number	Disease or group of diseases	Estimated prevalence (/100,000)
1335	Cantrell pentalogy	0.55*
562	McCune-Albright syndrome	0.55
811	Shwachman-Diamond syndrome	0.55**
449	Hepatoblastoma	0.54
79276	Acute intermittent porphyria	0.54
56	Alkaptonuria	0.5
848	Beta-thalassemia	0.5
213	Cystinosis	0.5**
35909	Combined deficiency of factor V and factor VIII	0.5
634	Netherton syndrome	0.5
682	Hyperkalemic periodic paralysis	0.5
122	Birt-Hogg-Dubé syndrome	0.5
661	Ondine syndrome	0.5**
782	Axenfeld-Rieger syndrome	0.5
611	Inclusion body myositis	0.49
101	Dentatorubral pallidoluysian atrophy	0.48
79264	Juvenile neuronal ceroid lipofuscinosis (Batten disease, Spielmeyer-Vogt CLN3 disease)	0.46
23	Argininosuccinic aciduria	0.45
3287	Takayasu arteritis	0.45
201	Cowden syndrome	0.45
902	Werner syndrome	0.45
169802	Severe haemophilia A	0.44
169808	Mild haemophilia A	0.44
857	Townes-Brocks syndrome	0.42**
256	Early-onset generalized limb-onset dystonia	0.4
258	Congenital muscular dystrophy type 1A	0.4
77293	Niemann-Pick disease type B	0.4
597	Central core disease	0.4
379	Chronic granulomatous disease	0.4**
88	Idiopathic aplastic anemia	0.4
582	Mucopolysaccharidosis type 4	0.4
42738	Congenital neutropenia	0.4
486	Severe Congenital neutropenia	0.4**
816	Sjögren-Larsson syndrome	0.4**
392	Holt-Oram syndrome	0.35*
510	Lesch-Nyhan syndrome	0.34**
327	Factor VII deficiency	0.33
140	Campomelic dysplasia	0.33**
2573	Moyamoya disease	0.33
565	Menkes disease	0.33**
83420	Proximal spinal muscular atrophy type 4	0.32
84	Fanconi anemia	0.3
255	Dopa-responsive dystonia	0.3
261	Emery-Dreifuss muscular dystrophy	0.3
845	Tay-Sachs disease	0.3**

ORPHA Number	Disease or group of diseases	Estimated prevalence (/100,000)
56970	Transmissible spongiform encephalopathy (generic term)	0.3
447	Paroxysmal nocturnal haemoglobinuria	0.3
2299	Aortic arch interruption	0.3**
90647	Long QT interval – deafness	0.3
676	Hereditary chronic pancreatitis	0.3
3004	Mirror polydactyly - vertebral segmentation - limbs defects	0.3**
534	Oculocerebrorenal syndrome (Lowe syndrome)	0.3**
79269	Sanfilippo syndrome type A (Mucopolysaccharidosis type 3A)	0.3
1300	Autosomal dominant popliteal pterygium syndrome	0.3
590	Congenital myasthenic syndromes	0.3
216694	Congenitally corrected transposition of the great arteries	0.3**
62	Alpha-sarcoglycanopathy	<0.3
219	Delta-sarcoglycanopathy	<0.3
143	Parathyroid carcinoma	0.28
75233	Wolman disease	0.28**
83419	Proximal spinal muscular atrophy type 3	0.26
45448	Miyoshi myopathy	0.26
702	Pelizaeus-Merzbacher disease	0.25
77292	Niemann-Pick disease type A	0.25**
528	Berardinelli lipodystrophy	0.25
3000	Familial gonadotropin-independent male-limited sexual precocity	0.25
678	Papillon-Lefèvre syndrome	0.25
99867	Thymoma	0.25
93476	Hurler-Scheie syndrome	0.23
910	Xeroderma pigmentosum	0.23**
324	Fabry disease	0.22**
169805	Moderately severe haemophilia A	0.22
277	Severe combined immunodeficiency due to adenosine deaminase deficiency	0.22
111	Barth syndrome	0.22
436	Hypophosphatasia	0.21**
37	Acrodermatitis enteropathica due to zinc deficiency	0.2
61	Alpha-mannosidosis	0.2**
209916	Extraskeletal myxoid chondrosarcoma	0.2
328	Congenital factor X deficiency	0.2
93598	Alanine-glyoxylate aminotransferase deficiency (hyperoxaluria type 1)	0.2
745	Protein C deficiency	0.2
743	Protein S deficiency	0.2
224	Neonatal diabetes mellitus	0.2
264	Autosomal dominant limb-girdle muscular dystrophy type 1B	0.2
99870	Letterer-Siwe disease	0.2
308	Unverricht-Lundborg disease	0.2

ORPHA Number	Disease or group of diseases	Estimated prevalence (/100,000)
3006	Pyridoxine-dependent epilepsy	0.2**
98850	Aggressive systemic mastocytosis	0.2
83463	Microtia	0.2
633	Short stature due to growth hormone resistance	0.2
95455	Epidermal necrolysis	0.2
98249	Ehlers-Danlos syndrome	0.2
93474	Scheie syndrome	0.2
353	Autosomal recessive limb-girdle muscular dystrophy type 2C	<0.2
3162	Sézary syndrome	0.18
1456	Atypical coarctation of aorta	0.17**
280219	Pelizaeus-Merzbacher disease, classic form	0.17
407	Non-ketotic hyperglycinemia	0.17
99874	Adult pulmonary Langerhans cell histiocytosis	0.17
583	Mucopolysaccharidosis type 6 (MPS6)	0.16**
335	Congenital fibrinogen deficiency	0.15
223	Nephrogenic diabetes insipidus	0.15
576	Mucolipidosis type 2	0.15**
2770	Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy	0.15
79430	Hermansky-Pudlak syndrome	0.15
118	Beta-mannosidosis	0.14
64	Alstrom syndrome	0.14
75840	Congenital muscular dystrophy, Ullrich type	0.13
268	Autosomal recessive limb-girdle muscular dystrophy type 2B	0.13
763	Pycnodysostosis	0.13
48818	Aceruloplasminemia	0.1
47	X-linked agammaglobulinemia	0.1
3329	Tibial aplasia - ectrodactyly	0.1
209341	Infant autosomal dominant proximal spinal muscular atrophy	0.1
209335	Adult-onset proximal spinal muscular atrophy, autosomal dominant	0.1
142	Anaplastic thyroid carcinoma	0.1
329	Congenital factor XI deficiency	0.1
326	Congenital factor V deficiency	0.1
225	Maternally-inherited diabetes and deafness	0.1
3156	Renal dysplasia – retinal aplasia	0.1
1775	Congenital Dyskeratosis	0.1
204	Creutzfeldt-Jakob disease	0.1
773	Refsum disease	0.1
367	Glycogen storage disease type 4	0.1**
93322	Tibial hemimelia	0.1
73274	Acquired haemophilia	0.1
411	Hyperlipoproteinemia type 1	0.1
31824	Colchicine poisoning	0.1
1018	Diffuse leiomyomatosis - Alport syndrome	0.1

ORPHA Number	Disease or group of diseases	Estimated prevalence (/100,000)
85834	Juvenile myelomonocytic leukaemia	0.1
512	Metachromatic leukodystrophy	0.1
98918	Acute motor axonal neuropathy	0.1
98917	Acute motor-sensory axonal neuropathy	0.1
2686	Cyclic neutropenia	0.1
3198	Stiff person syndrome	0.1
205	Crigler-Najjar syndrome	0.1**
298	Mitochondrial neurogastrointestinal encephalomyopathy	0.1
1959	Evans syndrome	0.1
231183	Usher syndrome type 3	0.1
906	Wiskott-Aldrich syndrome	0.1
47045	Familial cold urticaria	0.1
119	Beta-sarcoglycanopathy	<0.1
93314	Spondylometaphyseal dysplasia, Kozlowski type	<0.1
501	Lafora disease	<0.1
305	Junctional epidermolysis bullosa	0.06
1267	Botulism	0.05
178	Chordoma	0.05
331	Congenital factor XIII deficiency	0.05
325	Congenital factor II deficiency	0.05
77261	Gaucher disease type 3	0.05
2442	X-linked lymphoproliferative disease	0.05
337	Fibrodysplasia ossificans progressiva	0.05
2788	Osteoporosis - pseudoglioma	0.05
882	Tyrosinemia type 1	0.05
99718	Leber 'plus' disease	0.04
69087	Naegeli-Franceschetti-Jadassohn syndrome	0.035
147	Carbamoylphosphate synthetase deficiency	0.03
34520	Congenital muscular dystrophy with integrin deficiency	0.03
280210	Pelizaeus-Merzbacher disease, connatal form	0.03
280224	Pelizaeus-Merzbacher disease, transitional form	0.03
86882	Hepatosplenic T-cell lymphoma	0.03
290	Congenital rubella syndrome	0.03**
85212	Foetal Gaucher disease	0.01
77260	Gaucher disease type 2	0.01
584	Mucopolysaccharidosis type 7	0.01
740	Progeria	0.005
35	Propionic acidemia	0.002

Source: *Orphanet* (2013).

Caption: ** Prevalence at birth