Nationally-based organisation for rare cancers: the background for the European Reference Networks (ERNs)

A multiple case-study based on the experiences of Czech Republic, Finland, France, Italy, Lithuania and Spain

TASKS 2.1, WP10 – Deliverable 10.2

Joint Action on Rare Cancers (JARC)

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FOREWORD

This work was carried out in the framework of the Task 2.1 of the WP10 of the Joint Action on Rare Cancers (JARC). These findings are based on fieldwork undertaken in six European countries; they formed the basis of our investigation into the creation and working of national reference centres (NCR) or networks for rare cancers in the European health systems. Using sarcoma as an example, we tried to shed light on how organisational models and contextual factor influenced the establishment and functioning of NCR in Czech Republic, Finland, France, Italy, Lithuania and Spain. These country-based findings may guide and strengthen and provide guidance of the newly launched European Reference Networks (ERNs). This study is ultimately intended to inform the debate among European cancer patients, scientific societies and representatives of cancer plans in order to generate recommendations on rare cancer care organisation at national level that could be relevant at the EU level.

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JOINT ACTION ON RARE CANCERS

Description

The Joint Action on Rare Cancers (JARC) is aimed to integrate and maximize efforts of the European Union (EU) Commission, EU Member States and all stakeholders to advance quality of care and research on rare cancers.

The public health challenges posed by rare cancers include the limited professional expertise in the community, the difficulties in clinical research, the need of a timely and appropriate diagnosis and optimal treatment from the very beginning of the patient’s journey. An accurate clinical, pathologic and biological assessment of the disease of the individual patient is key to survival and cure, as well as an expert clinical decision provided by a multidisciplinary team. To this end, proper referral of patients and effective clinical networking are crucial in rare cancers. This is the main reason why JARC decided to shape its efforts around the new European Reference Networks (ERNs) with the following objectives:

1. Improving epidemiological surveillance of rare cancers in the EU
2. Identifying standards of care for all families of rare cancers to ensure sharing of best practices and equality of care for rare cancers across Europe, particularly through clinical networking
3. Improving the implementation at local level and within ERNs of clinical practice guidelines on rare cancers
4. Promoting integration of translational research innovations into rare cancer care
5. Improving education on rare cancers for medical and non-medical experts to ameliorate management of rare cancers and to improve rare cancer patients’ empowerment in the EU
6. Identifying core strategies to incorporate in National cancer plans and Rare disease plans to address the specific needs of rare cancers across EU MSs.

The JARC is structured in 10 work packages (WPs). Three cross cutting WPs (WP1 coordination, WP2 dissemination, WP3 evaluation) and 7 specific WPs based on the JARC objectives: WP4 epidemiology, WP5 quality of care, WP6 clinical practice guidelines, WP7 innovation and access to innovation, WP8 medical education, WP9 childhood cancers and, WP10 rare cancers policy. Patients work across all work packages, driving the JARC efforts along the needs of the only end users of all what we can do, in care and research as well.

This deliverable was included in the WP10 Health Policy and the objective was to assess the designation and marketing process of the Orphan medicinal drugs for rare cancers. The leader of this task was the Catalan Institute of Oncology (ICO).

Contributors to this report: Joan Prades (ICO), Josep M Borras (ICO).

Work Package 10. Health policy

Governments use National Cancer Plans (NCPs) to articulate their goals and implementation strategies on cancer control. A review of their main objectives was carried out in the EPAAC Joint Action, and we plan to build on that work in order to understand the specific proposals and strategies made at the national level regarding the formulation and implementation of rare cancer/diseases policies, including the commonalities and divergences between such
policies. Two approaches are included in its development. On one side, WP10 is intended to assess the potential to develop criteria to harmonize rare cancer planning and coordination, with a view to streamlining strategies and measures to be proposed to Member States at the national level for rare cancers. On the other, WP10 will highlight the main open political issues on the EU agenda of relevance to rare cancers and, specifically, those policy recommendations aimed at raising awareness about the issues surrounding rare cancer care, thereby suggesting stakeholder action and public policies both at the EU and national levels.

The development of ERNs makes this exercise relevant, as it will shed light on the potential for positive synergies between measures targeting rare diseases at national and EU levels. WP10 will build on and integrate the outcomes from all WPs related to policy recommendations in order to compile them through a common framework.

Aim and purpose of deliverable

The Joint Action on Rare Cancers (JARC) is a partnership among EU countries, the European Commission, scientific societies, patients, industry and other stakeholders with the aim of contributing to improve health outcomes for patients with rare cancers in the EU and to decrease health inequalities across EU countries. Strategically, maximizing chances of European Reference networks (ERNs) for rare cancers to be successful is seen as a key factor.

One specific objective, which is the aim of this deliverable, was to analyse different nationally based hospitals or networks for rare cancers in the context of their inclusion within the ERNs.

The target group of the specific deliverable

Policy makers, cancer plans, and rare diseases’ plans.

Summary of the main conclusions of the deliverable

The challenges posed by rare cancers and rare cancers organisation and policy are very relevant and recognized by all stakeholders. The main conclusions of the study were as follows:

- Singling out National Reference Centres (NRCs) across the six geographies tested requires these centres to play a **leading role in the diagnostic-therapeutic processes of all rare cancer patients**. Even though an informal reputation as a centre of excellence carries significant weight, health systems can be further strengthened in three ways: (1) awarding specific legal status or institutional recognition to expert centres; (2) targeting funding based on specialised services and units; and, (3) establishing a quality control and accreditation system to maintain accountability.

- Officially appointing NRCs at a national level enables **clinical expertise in rare cancers to be identified and benchmarked**. The key components of this approach rely on: first, centralisation of clinical decision making to expert centres as well as clinical research and guidance on sources of critical evidence to be used. Second, a cooperation model that defines the relationships and communication methods between expert centres and other health providers, with a view to enabling agile clinical advice or patient referrals. Third, defining the expertise level of non-specialised centres as not all of them have the minimum expertise to coordinate with expert centres and provide treatments.
- Equal access to quality care for sarcoma patients requires expert anatomopathology diagnosis from the outset. While accurate diagnosis is critical for patient treatment and prognosis, practitioners working outside expert centres must receive ongoing practical training to avoid taking needle biopsies. Enabling expert diagnosis is strongly recommended in health systems.

- Planning of expert centres and medical services for rare cancers should be related to patient volumes while maintaining insight into pathology subtypes (e.g. bone sarcoma, retroperitoneal liposarcoma). There are various examples of health services reorganisation and sub-specialisation according to the different sarcoma subtypes. However this specialisation is often lost in the generic label of ‘reference centre’ or ‘university hospital’. Once clinical expertise is clearly signposted, at a sub-pathological level, all practitioners will be aware of where to refer specialist cases.

- A network model, where patients are proactively coordinated and linked to long distance treatment via inter-hospital exchange, requires additional funding for NCRs. This extra funding would also support highly specialised services in NRCs such as molecular diagnosis, innovative and multi-modal treatments, which are more costly than the ‘standard care’ provided in non-specialised settings. Additional financing should be linked to the definition and assignation of NRC status.

- Scientific societies and especially sarcoma groups should form a strategic part of the governance of highly specialised services for rare cancers whether it is intended to set up expert networks of NCRs. Selecting and evaluating medical centres against quality standards implies important costs in terms of knowledge management which may be tackled by health authorities in collaboration with expert professionals. However, creating a network of expert centres requires linking the clinical decision-making frameworks to the needs for information sharing and knowledge transfer between expert practitioners (e.g. implementing a national tumour board on Ewing sarcoma). The different areas of expertise and therefore clinical roles of expert teams in the context of a network are inherent to a successful, formal network of expert centres.

- The centralisation of patients in expert centres (or remote verification of clinical decision making), when coupled with clearly recognised NRCs, results in better access to expert advice and a well-organised sequencing of diagnosis-to-treatment process. Equity in access to quality care can also be considered in terms of clinical trials’ enrolment.

- In addition to quality of care assessment, external evaluation of expert centres provides an important opportunity to benchmark quality of care and scientific research rather than patient volumes solely. In parallel, external evaluation can assist in standardizing care processes and structures across expert centres.

- Health systems where expert centres lack specific status and a guidance role may limit the ERNs ability reach all patients across the country. Poor coordination at a national level has a European-wide impact as knowledge share and transfer is not ingrained across expert clinical environments. Moreover, a lack of nationally coordinated specialisation may create inequality for rare cancer patients, depending on where they are treated, which for many of them still means a non-expert centre close to home.
I. INTRODUCTION

There is broad consensus that networking is the most appropriate answer to the many issues pertaining to rare cancer care. The creation of European reference networks (ERNs) provides a clear window of opportunity to improve rare cancer care in Europe, potentially representing a comprehensive intervention across many different areas, including quality of care, research, education, prevention, diagnosis and treatment.

The implementation of ERNs is underpinned by national centres and/or networks of reference hospitals for rare cancers and implies for them the adoption of a different organisational approach. However, while the streamlining procedures and the general requirements for the establishment of ERNs are standard for all EU member states, contextual factors at national level entail different advantages and implications for the ERNs. Indeed, there is important variability in the level of clinical integration in each country and particularly in the existing ties among clinicians, expert teams, centres and patient organisations at a national level. Furthermore, the nationally based centres and/or networks might show different levels of involvement and implementation of all the decision-making processes regarding rare cancers in the context of ERNs.

There are several centre- and network-based experiences at a national level that could provide lessons for the implementation of ERNs. As ERNs will be embedded in different settings, these should be envisaged as key levers for full ERN development. Thus, it seemed reasonable to focus on formal country experiences in order to better understand the keys to building successful networks for rare cancers at European level.

This study was aimed to providing an in-depth understanding of national experiences and their connection with the developing ERNs based on the perspective of physicians, clinical managers and patients. They may gather relevant perspectives on how different European countries conceive and use the ERNs.
II. OBJECTIVES AND RESEARCH QUESTIONS

Main research questions

What are the relevant organisational and clinical management features at nationally based centres for rare cancers?

How have national reference centres been embedded in the health system? What lessons can be learnt from their implementation?

General and specific research objectives of the study

General purpose

To analyse different nationally based hospitals or networks for rare cancers in the context of their inclusion within the ERNs.

Specific aims

- To analyse the processes through which national reference hospitals are embedded at national health system.
- To understand the organisational settings that enable patients to equitably access to experts centres at national level.
- To understand the interaction between national and European guidelines and how the knowledge transfer is performed.
- To analyse the extent to which national mechanisms for cooperation and governance are perceived to change the relationships between national providers and its potential implications for ERNs development.
- To identify the added value of ERNs and the potential opportunities they bring for improving rare cancer care at a national level.
III. METHODOLOGY

Study design
We adopted a case-study design based on the analysis of six nationally-based experiences on establishing expert centres for rare cancers.¹ The case study facilitates the understanding of complex phenomena by identifying and detangling the influences and roles played by contextual variables.² The limited number of cases is justified by the need to achieve a comprehensive understanding of comparable cases through different qualitative research strategies. The case study applies mixed methods, with a qualitative study, case-site observation and material collection. In order to contribute to standardising the context for analysis, we focused on one example of a rare tumour such as sarcoma. This disease shows a significant degree of organisation and services specialisation as well as academic groups at national level.

The qualitative study consisted of semi-structured interviews (annex 1) conducted during on-site visits at different European countries; the fieldwork was carried out from February to July, 2018 (Figure 1). Before embarking on fieldwork the health authority of participating countries received a study protocol and a ‘how-to’ guide for the research (annex 2). At the start of each face-to-face interview, participants were given general information about the study and an Information Sheet which explained the objectives of the research (annex 3). Participants were asked to sign a consent form and were advised that all information given during interviews would remain confidential (annex 4).

Sample strategy
We used purposive sampling strategy and selected informants following the criterion of discourse representativeness. The sample for each selected case/country involved: (1) informants from two different centres at national level; (2) physicians from different specialties dealing with sarcoma, including clinical leaders and managers involved in the launch of ERNs; (3) patient organisation representatives (EPAGs), and (4) leaders of ERNs and European policymakers involved in the ERNs’ launch. En total se llevaron a cabo 52 entrevistas, incluyendo los siguientes perfiles: Medical oncologist (n=10), radiation oncologist (n=4), surgeon (n=8), pathologist (n=5), radiologist (n=2), geneticist (n=2), nurses (n=3), patients’ representative (n=7), technicians from Ministries of Health or other public bodies (n=9) and European policymaker (n=2).

The national experiences selected for the case studies were: Czech Republic, France, Finland, Italy, Lithuania and Spain. The inclusion criteria related to the research objectives were the following:

- National centres providing care for sarcoma and included in the European reference network for adult solid cancers (ERN-EURACAN).

Both officially and non-officially recognised experts’ centres at national level.

Mature national experiences, with a relatively homogeneous disease-based community of physicians, clinical researchers and patients.

Figure 1. Onsite-visits conducted from February to July, 2018.

Data analysis

We first identified the thematic areas related to nationally-based centres and networks for rare cancers. These were: designation and role national authorities, clinical organisation and connection with the ERNs. We then performed a thematic analysis, grouping data into codes and categories to allow a narrative description. This identification enabled the extraction and organisation of data regarding the content of interviews. We used the Atlas.ti software package (v6.2, 2011) to collect and organise data.

Limitations

As with all qualitative studies, our research focused on the views of key informants, thereby implicitly ruling out the possibility of capturing all the experiences and best practices that might exist in the health system. Also, the list of informants was based on proposals put forward by National Authorities and representatives per country within JARC, which could have biased the selection of informants towards those representing showing better experiences. The selection criteria regarding the different profiles, plus the fact that two centres per country were involved, were intended to minimise this limitation. Another limitation was that healthcare professionals from non-expert centres were not interviewed. Finally, two of six countries did not provide the number of informants required.
IV. RESULTS

1. THE STATUS AND ROLE OF NATIONAL REFERENCE CENTRES

The national reference centre as a single institution at national level

1.1 Status of national reference centres for rare cancers

Among the countries analysed, France and Spain are the only ones to have assigned a specific legal status to centres treating rare cancers; in both cases, this occurred before the launch of the European reference networks (ERNs). In France, the instrument that formally established ‘rare cancer reference centres’ was the Cancer Control Plan 2009–2013. One relevant aspect of the French experience is that they developed clinical networks – 23 to start – within which the reference centres had to operate in order to extend access to expertise to all patients of rare cancers. The clinical network for sarcoma was called NETSARC. Anatomopathology networks were also institutionalised in order to achieve the objective of expert pathology double-reading. The coverage rate of this network for sarcoma (called RRePS) is 80%, according to the professionals interviewed. Another point of note is that the French centres, within the framework of the clinical networks, are organised on two levels: competent centres and expert centres (see section 2.1); the latter are characterised by their scientific leadership.

With regard to Spain, a Royal Decree established the general procedure for designating Centres, Services and Units of Reference (CSUR) in 2006, with the same objectives as in the French networks: improving equity in access to highly specialised services for different pathologies and uncommon procedures. In the case of sarcoma, there were five accredited CSURs for adult cases and four for paediatric sarcomas. As in France, in Spain the health authorities – encompassing those at both the State and Regional level – are responsible for identifying the pathologies included in this system. By contrast, in Spain there is no network or entity led by professionals that regulates and coordinates the different centres. It is the Ministry of Health (MoH), working through a committee of experts and representatives in the different regions, that evaluates and accredits the candidate centres or units.

Finland and the Czech Republic are in a different legal situation. Some of their expert centres in sarcoma or rare cancers are reference centres at the European level owing to their participation in the ERNs, but at the country level, expert centres do not have a specific legal status.

Italy and Lithuania are somewhere between these two realities. The former has taken a relevant legal step with the ‘State-Regions Agreement’ signed in 2017. This measure institutionalised the National Network of Rare Tumours (RNRT in its Italian abbreviation) as the actor responsible for identifying expert centres at a national level and provided an outlet for the assessment and accreditation process focused on quality “that goes beyond the requirements of the ERNs”. This network, which is an evolution of an older network for rare adult tumours (RTR in its Italian abbreviation), includes the participation of the State, whose
involvement comes in the form of an agency (AGENAS) in charge of the functional coordination of the network. The RTR, by contrast, was based solely on professional collaboration. However, these mechanisms – including accreditation – have not yet been fully realised, and today it is not possible to identify a stable system of expert centres in the country.

For its part, Lithuania changed the legal denomination of ‘competent centres’ to ‘national reference centres’ (NRCs) in 2015, based on the centres identified and accredited during the National Plan on Rare Diseases. However, this legal change was challenged in court because it limited the de facto constitutional right of patients to be treated in any healthcare centre. The lack of a specific legal status could have negative implications, leading to the duplication of specialised services in a context of a country with only 3 million inhabitants. The aversion of non-specialised clinicians and policy-makers to associating the legal status of expert centres to the concentration of cases is not unique to Lithuania. For example, the pathology double-reading in France was initially obligatory, while in current practice, it is more like a ‘strong recommendation’.

1.2 Designation and selection process of national reference centres

The designation of expert centres varies by country in terms of its degree of formalisation, but also with regard to its links to the process of European accreditation. On the one hand, examples of non-specific designations are found in Finland and the Czech Republic, where the ‘expert centre’ label is related to being a university hospital and having highly specialised services and a high patient volume, but not to a specific process of selection and accreditation.

In Lithuania the official title of ‘reference centre’ was implemented in explicit alignment with the eligibility criteria for ERN candidate centres in order to avoid the existence of a dual accreditation system. Following the suspension mentioned above, the criteria used were those of the National Plan on Rare Diseases. Given the small population of the country, the criteria for joining the ERNs “were really difficult to achieve”.

On the other hand, Spain presents a high level of formalisation in the selection of NRCs. The MoH selects candidates using an accreditation system based on two evaluation phases: (1) self-assessment and provision of documentation by the centres and (2) external audit, including an on-site visit. Following evaluation by an expert committee, representatives of the Regions and the MoH, a proposal is made to the Interterritorial Counsel, a federal political body that approves the designation of the centres and opens the door to their candidacy. Accreditation should be renewed every five years. For its part, Italy is in the middle of a transition toward a system resembling the Spanish one, at least from the perspective of the State: this actor will be the guarantor of the accreditation of the centres and will implement a specific system of accreditation based on indicators, databases, etc. However, the expert centres will operate within an institutionalised network, aimed at ensuring the maximum possible equity of access for these types of patients. The main desire is for stricter criteria than in the European system, so that “the real quality of care can be verified in each centre”.

In France, the selection of centres that make up the national clinical networks depends on the leaders and the consensus reached within the networks themselves. The tacit process of member selection is based on criteria like patient volume, scientific activity and the existence
of a tumour board that covers all stages of the care process. The MoH validates these decisions.

In addition, European statutes require ERN candidate centres to have the prior endorsement of their respective ministries. This condition has been criticised by some countries because despite interest and local actions to identify reference centres in rare cancers, in some countries European organisational demands have moved more quickly than at the country level.

1.3 Funding of national reference centres
Financing the NRCs is related to their status within different health systems, but it cannot be taken for granted. For example, France is the only country where the health authorities specifically allocate funding for reference centres, distributing funds through the network made up of expert centres and competent centres. Moreover, the three expert centres are provided with a clinical research assistant who, among other tasks, maintains the database and analyses the activity of the network. The financial provisions cover at least the clinical (NETSARC) and pathology (RRePS) networks; as double-reading is a specific policy in France, the centres that implement it are compensated. Only the three expert centres in sarcoma can carry out early stage clinical trials.

Specific financing exists neither in Italy nor Spain, but in the former, reimbursement is stipulated as part of the State-Regions Agreement. In Spain, this deficit complicates the registry of information related to accreditation, which ends up being resolved through personal efforts.

In Lithuania, Finland, and the Czech Republic, the expert centres do not have extra financing. Interviewees argued that this situation is problematic because rare cancer patients are a financially demanding group, and the greater visibility of expert centres at a national level accelerates referrals to these centres.

NRCs as a system of expert professionals

1.4 Clinical care- and research-based collaboration in national reference centres
Collaboration between reference centres has been analysed to determine the extent to which these centres form an expert system. The reasons for collaborating respond to organisational strategies and the role of the health authorities, but also to aspects related to the availability of services. For example, centres may not be experts in all subtypes of sarcoma or able to provide a very specific procedure (e.g. intra-arterial chemotherapy). These concerns justify collaboration at both a clinical and scientific level.

Two countries, France and Italy, stand out for the level of collaboration between expert centres. In the first case, collaboration is continuous thanks to the total integration between the healthcare system, made up of different networks (NETSARC, ResOs, RRePS), and the expert network based in the pathology society, the French Sarcoma Group. The nexus of all these actors is a coordination instrument called Inter-SARC. It is worth highlighting the
flexibility that exists between expert levels across the network and how it can adapt to the needs and challenges posed by the pathology. For example, in the case of Ewing’s sarcoma, there is a national tumour board that convenes once a month to discuss the most difficult cases. Another feature of note is that the pathology network does not only handle the double-readings in cases from non-expert centres, it has also established a third reading among expert centres during a monthly meeting held in Paris to discuss the most complicated cases. In this context, network collaboration is favoured by the existence of a software platform that includes a shared database for the registry of activities.

For its part, Italy presents an important tradition of collaboration between expert clinicians and leading centres like the Istituto Ortopedico Rizzoli of Bologna and the Istituto Nazionale Tumori di Milano. This history is rooted in the network of rare tumours in adults (RTR). The collaboration between centres does not depend on the instruments of the network but rather on the relationships between professionals and their knowledge of the specialised services and open clinical trials in other centres. The network has a computer platform that enables communication with expert centres, among other functions.

In the Czech Republic, Spain, Finland and Lithuania, ties between expert centres are mainly based on personal relationships and/or their willingness to share cases that are difficult, or which require a very specific technique that may not be available in a given centre. In these countries, the model of cooperation is based on independent centres that can collaborate in one or more stages of the clinical process – diagnosis, treatment, clinical research – with intensities that vary according to the traditional links between the centres or the complexity of the cases. It is not unusual for expert centres to exchange images or pathological samples, or for them to refer patients for a clinical trial. In Lithuania, there are moves to assign the two expert centres in Vilna and Kaunas with the role of leader or collaborator for every pathology, according to the centres’ specific strengths. In any case, there is room for improvement with regard to collaboration in these four countries; paradoxically, it can be easier to find examples of videoconferences with international partners than with other expert centres in the same country.

In the area of clinical research, the present study could identify only one network of expert professionals that maintained a website of all open clinical trials in the country along with an alert system to publicise new trials: the paediatric oncology network in France.

1.5 Clinical knowledge transfer between national reference centres

For a rare pathology like sarcoma, it is very desirable that reference centres within a single health system work according to the same clinical practice guideline (CPG) or set of recommendations and achieve an effective knowledge transfer. Factors like diagnostic complexity, surgical difficulties – of the utmost importance in bone sarcoma – and the need to link many medical treatments to clinical trials justify this arrangement.

With the exception of France – due to its formal network model – and of experiences associated with specific pathological subtypes, like the harmonisation of the clinical protocol for bone sarcoma in the Czech Republic, national expert centres do not use common CPGs as the first source of evidence. Instead, centres use national guidelines developed by scientific and disease-specific societies, the NCCN guidelines from the USA, and especially the guidelines
produced by the European Society of Medical Oncology (ESMO). Moreover, the recent formulation of ESMO-EURACAN recommendations on knowledge transfer between the European and national level was very pertinent. This not only because of the consensus content itself, but because there are experts participating in the development of clinical recommendations at a national level – for example, in the framework of societies for different diseases – and they are simultaneously performing a similar role at the ESMO-EURACAN level. In this way, the activity of the ERNs generates cohesion among experts at both a national and European level.

That said, in terms of clinical knowledge transfer at a national level and of overcoming the organisational and geographical barriers that separate professionals, the role of scientific societies, and especially academic-scientific groups focusing on a single pathology, cannot be understated. These groups are: the Italian Sarcoma Group (www.italiansarcomagroup.org), the Scandinavian Sarcoma Group (www.ssg-org.net), the French Sarcoma Group (GSF-GETO) (www.infosarcomes.org/gsf-geto), the Spanish Research Group on Sarcoma (GEIS) (www.grupogeis.org), the Czech Cancer Society, and the different scientific societies that are active in Lithuania. These groups contribute to the continuous exchange of information and the generation of consensus among experts, which then are translated into clinical practice.

In fact, in addition to France, the communication channels between the healthcare network and the disease societies are very evident in other countries. For example, the Czech Cancer Society hosts discussions on clinical outcomes in different centres or on controversial issues such as the concentration of services. As mentioned above, this group has also facilitated consensus on which CPG to use among the reference centres treating bone sarcoma. For its part, the French Bone Sarcoma Group (ResOs) is the reference for professionals wishing to identify new clinical trials.

National experts were also asked if any type of clinical guidance had been established by the reference centres for other hospitals. This aspect was considered especially crucial because no matter how centralised the treatment for a disease is, other hospitals and care levels continue to have an essential role identifying and referring suspected cases. It is well known that a patient’s prognosis and access to a wide range of treatments depends on their early referral to an appropriate centre. Thus, for countries like Finland or the Czech Republic, the expert centres should endorse the guideline or protocol of reference for the health system as a whole.
2. ACCESS TO AND CLINICAL ORGANISATION OF EXPERT CARE

2.1 National reference centres: services organisation

Do expert centres at a national level have an organisational structure that is different from the rest of the centres treating sarcoma? Three relevant dimensions emerge: (1) multidisciplinary specialisation at the subpathology level; (2) the establishment of care pathways; and (3) the importance of expert centres being able to provide comprehensive care.

(1) Being an expert centre was positively associated with having a multidisciplinary and integrated organisation. However, when these qualities were accompanied by a high patient volume, professional specialisation extended to the subpathology level. Therefore, we identified experts in soft tissue, bone or spine sarcoma, and consequently clinical decision-making was managed by multidisciplinary care teams specialising in those subareas. Moreover, this subspecialisation of the services and teams has entailed the designation of professionals responsible for diagnostic, treatment or research consultations, such as in the Memorial Masaryk Cancer Institute (Czech Republic). All the countries participating in the study have at least one centre with clinical units or tumour boards of these characteristics. In the case of Lithuania, clinical organisation is framed at the tertiary level, in competent centres, which are defined as functional units that integrate all the professionals involved and which are supported by a fixed structure made up of a clinical coordinator, a nurse, and administrative support.

(2) Variations in clinical practice between hospitals is seen as a relevant problem in the area of rare cancers. Countries have responded, for example in Finland, by implementing health system reforms to establish common care pathways in five university hospitals to guarantee higher quality and standardised care. Increased, shared integration would entail, for example, performing the same diagnostic procedures for all cases of suspected sarcoma or guaranteeing treatment within a certain time for specific pathologies. In France, in fact, the subdivision between expert centres and competent centres entails that the former should establish the diagnostic and treatment processes, while the latter should follow them; the implementation of these processes is only partial.

(3) In the Czech Republic, there is a need for expert centres to also be comprehensive care centres for patients. The low care continuity and the jumps between care levels and hospitals during the diagnostic and treatment process make the care journey very difficult for some patients. Comprehensiveness would mean being the first source of information about the pathology – which also has implications in the international sphere –, responding to all patient needs (not just their clinical requirements), or involving in some way national or international patient associations.

2.2 Centralisation of cases

The identification of reference centres is associated with – but not contingent to – the idea that all patients can benefit from their care. Thus, the centralisation of cases is assumed to be related to better clinical outcomes. However, the dispersion in the provision of sarcoma treatments in non-expert centres, not to mention the accidental interventions that typically
occur in superficial soft tissue sarcomas, is considered excessive in almost all the countries included in the study. This could compromise the quality of care that patients receive.

None of the countries analysed used measures to enforce the centralisation of sarcoma cases in reference centres. However, when clinical networks were set up in France, the clinical consultation with expert centres was mandatory. At the regional level, Catalonia (Spain) has implemented measures to foster centralisation, such as not reimbursing treatments provided outside of expert centres.

**Degree of centralisation of sarcoma patients in expert centres**

There is considerable variation in the degree of centralisation of sarcoma patients in expert centres among included countries, according to figures provided by professionals. In France, for example, pathology double-reading that is led by competent or expert centres has a coverage of 80% in sarcoma, and the percentage of discordant readings is approximately 15%, according to professionals. Likewise, around 40% of the patients are treated in hospitals outside the network of experts. By contrast, over 90% of sarcoma patients are treated in expert centres in Lithuania, not only because of the size of the country, but also because of the highly organised health system (e.g. fast track access for complex pathologies to the tertiary centres in Vilna and Kaunas).

In Spain, there are no data on coverage, in part because health system administration has been devolved to the regions, but it is the MoH that has established the expert centres. Something similar occurs in Finland with the partial regionalisation of health services at a municipal level – although the Finnish case differs because a ministerial decree restricts treatment for sarcoma cases to the five existing university hospitals. Thus, although not all of these hospitals can be considered expert centres in all sarcoma subtypes, patients always receive treatment in university hospitals. On the contrary, in the Czech Republic, there is also a ministerial decree that restricts treatment for patients with rare cancers to the 15 comprehensive cancer centres (CCCs) distributed throughout the country, including the two centres that are truly experts in sarcoma in Prague and Brno. However, according to professionals, about 30% of patients are treated in lower-level hospitals, and just three or four centres treat more than 30 cases per year.

In Italy professionals are concerned by the low level of centralisation of sarcoma cases in expert centres. According to our informants, at least 40% of the patients are treated outside of these hospitals. This contrasts with the pathological diagnosis, which is mainly centralised in the University Hospital of Treviso. Looking ahead, in the area of anatomical pathology, professionals perceive that “the priority for Italy should not be the promotion of a second opinion, but rather that a group of expert pathologists guarantee the quality of the first opinion” (apart from in the Hospital of Treviso, presumably).

**The concept of ‘reference centre’ for a pathology: an important limitation**

The fact that a centre is defined as being a ‘reference’ in sarcoma at national or European level does not imply that its expertise is uniform across all pathology subtypes. In fact, some professionals warn that referring cases to an expert centre simply because clinicians consider it to be one can be risky. Thus, Lithuania is working to centralise better rather than more, for example, by elevating outstanding professionals who specialise in certain techniques or rare
cancers, centralising the indication of very specific treatments to a single centre, and systematically sending all samples to a truly expert centre in anatomical pathology. In Finland professionals supported the need to explicitly promote and strengthen expert centres through a policy for centralising cases. For example, all the professionals interviewed recognised the University Hospital of Helsinki as having the most expertise in bone sarcoma, but this centre does not have any specific recognition beyond its own prestige.

**Diagnosis and geography**

Countries like the Czech Republic or Italy have geographical areas that have especially low coverage, as they have no links to EURACAN centres or to hospitals considered to be expert centres at a national level. This situation has led the Italian health authorities to propose the creation of expert centre(s) in the south, thereby reducing the currently massive healthcare migration to central and northern parts of the country. Spain has a similar problem, as accredited centres are located primarily in Madrid, Barcelona, Seville and Valencia, while elsewhere they are practically absent. In recognition of this fact, the MoH has developed specific protocols on the care processes to be followed by hospitals who attend cases in regions with little coverage.

Some professionals highlighted that “it is more probable that patients in the catchment area of an expert centre present at the stage of suspicion than those referred from other centres”. This could be a problem to the extent that it reflects the lack of awareness and knowledge among professionals, who rush to perform a needle biopsy; this situation occurs in all the countries analysed. That said, this phenomenon is also subject to some variations: the most important differences are within each country, where there are regions whose professionals have worked through scientific societies or networks to transmit the importance of referring patients with suspected sarcoma for expert diagnosis. Continuous education and awareness campaigns in all health system actors who may diagnose a sarcoma are essential in limiting inappropriate diagnoses.

**2.3 Care coordination and management of patient referral to/from national reference centres**

Beyond the coordination that may exist between reference centres (see section 1.4), another critical element to improve patient access is their collaboration with other centres in the health system. The differential diagnosis is crucial so that patients and their families do not spend months or years trying to find a diagnosis, compromising the range of treatment choices and the prognosis. At the same time, there are patients who only want to receive treatment in the hospital nearest to their home.

It is not unusual for care processes to be split between expert centres and other hospitals in order to mitigate the social costs related to distance, age and/or the health condition of patients. The analysis of these relations has allowed the identification of three different models:

**Market model**

There are different expert centres, but in the absence of stable and formal inter-hospital relationships, the attending physician must decide where to refer the patient. Referral
decisions are based on the ‘trust-perceived quality’ binomial, although informal relationships between clinicians are also important, as is the appropriate reception of patient referrals in the expert centre (Czech Republic, Finland, Lithuania, Spain).

The particularities of each country are as follows:

-Czech Republic: fluid relationships between expert centres and other hospitals in the shared management of patients (referral, acute complications) depending on the history of ties between centres. In some regions of the country, there is a more consolidated tradition of cooperation than in others.

-Finland: frequent coordination between clinicians at hospitals of different levels, with a particular emphasis on the use of video-conferencing and the avoidance of travel for patients (e.g. shared management of the diagnostic process or follow-up).

-Lithuania: shared management with other centres is not usual due to the size of the country; care is centralised in expert centres. Fast-access circuits have been established to refer complex pathologies to tertiary centres in Vilna and Kaunas; these can be accessed from any point in the health system.

-Spain: there is great variability with regard to collaboration with expert centres, resulting in differences in care continuity. Some network formations can be identified in the professional sphere (e.g. pathologists or oncologists who collaborate with each other on difficult cases).

**Network model**

Expert centres act as central nodes within a stable system of inter-hospital relationships, incorporating formal care instruments to ensure patient access and continuity of care. The referring centre may choose the expert centre where they send patients, but the relationships between centres are organised on the basis of geography, through pathologists and expert tumour boards (France).

Some of the key features of this organisational model are:

- Once the double-reading is complete, the attending physician can send the patient’s case for discussion in a competent or expert centre. The pathologist is not neutral in this process but can propose that the case be referred to an expert centre in case of a complex subtype; in any case the non-expert professionals “are supposed to systematically ask for advice for every patient”.

- The expert multidisciplinary tumour boards are charged with providing medical advice – clearly, regarding the proposed treatment plan – to professionals working in non-expert centres.

- The report produced following the evaluation sometimes recommends that the patient be referred to an expert centre in order to guarantee the maximum quality or to administer an innovative treatment that is not available in the hospital nearest to the patient’s home.
- The discussion of a patient from another hospital has limitations because “sometimes it’s difficult to really send good advice without having seen the patient”. Implicit in this concern are the differences existing between centres regarding the technical questions and quality in the pathological and radiological diagnosis, which makes it difficult to adjust the proposed treatment plan. Requests are often made to the centres to refer patients for an outpatient visit in order to perform a complete assessment. This situation can entail delays.

**Hybrid model**

This model combines freedom of choice in terms of the expert centre in which to receive treatment with a network guaranteeing processes of coordination and shared management of patients. Referral decisions are based in part on the network structure and in part on factors deriving from the market model, like trust and personal relationships (Italy).

Some of the key features of this organisational model are as follows:

- Expert centres systematically repeat the pathological diagnosis in patients referred to them.

- Due to the strong flow of medical migrants and the geographical distances, coordination with the patient’s usual hospital in the delivery of some treatments is commonplace. This issue has led to the projected creation of ‘treatment centres’, as “not all hospitals that refer patients can be spokes”. The spokes of this model would then be centres able to deliver quality medical treatments and effectively manage adverse effects and acute complications.

- In this type of relationship, there is an implicit hierarchy in which the expert centre is in charge of supervising the process as a whole.

The market model can present tremendous differences in terms of shared patient management and transfer of expert knowledge; this is due to the lack of a defined role for expert centres within the hospital system as a whole. Obviously, there are exceptions to this statement in the form of good collaboration practices in countries using this model.

This situation could also be interpreted in another way. The fact that expert centres are “hermetic” in relation to the rest of the hospitals limits the transfer of information about referred patients as well as the possibilities for learning and professional exchanges. Often the expert centre “captures patients” and disconnects them from their typical healthcare circuit, without establishing any type of collaboration with the referring centre.

Finally, one Italian doctor stressed that the idea is not to collaborate just for the sake of collaboration. The centres analysed in all six countries included in this study subscribe to the idea that treatments delivered in expert centres are of generally higher quality than those provided in a non-expert setting. Therefore, the network model should not justify the fact that a patient is treated in a suboptimal way. In this line, an informant from the Czech Republic commented that “it’s good to coordinate with other centres in the management of an acute complication, but it would have been less likely to happen in the first place in an expert centre”.

20
2.4 Travel and accommodation costs

Travel costs to the reference centres are important for improving patients’ access to these. Only Finland covers these expenses systematically, although this is conditional to costs exceeding 650€ annually; however, this offer is valid for any centre of the patient’s choosing. With regard to reimbursement policies, the existing legislation differs across the countries studied. In France and Spain, these expenses are expected to be covered, but application of the law is uneven and limited by a significant administrative burden. In Italy and the Czech Republic, no travel costs are covered, although some charities help to fill the gap for patients with limited resources. In Lithuania, the size of the country keeps this issue from posing a problem. On the other hand, patients point out that no country covers accommodation costs, which disadvantages patients who are far from a reference centre, especially when they have to undergo many diagnostic tests on different days.

A Spanish clinician saw this issue as a critical source of inequity. If patients do not have economic support, professionals may not bother to refer them to an expert centre, and they could falsely believe that the patient’s prognosis is poor. Thus, the question of covering travel costs may interfere in clinical decision-making, acting as a barrier and generating inequities among patients based on their place of residence.
3. POLICY ENVIRONMENT FOR NATIONAL REFERENCE CENTRES

The implementation of reference centres in different countries takes place within a particular context, subject to a specific regulatory framework. This is not only relevant in the implementation of the change – the creation of reference centres – but also in their sustainability. Three dimensions of the policy environment are especially relevant.

3.1 Clinical accountability and quality assessment

The identification of expert centres and their accreditation is an institutional space under construction; except for Spain and France, the centres lack a system for external assessment of clinical outcomes and care quality – understood here as the set of care processes. However, this is a relevant element for professionals, as they cannot self-declare themselves to be experts. Moreover, in the current context of moderate concentration of cases in expert centres, it is more important than ever to understand the differences between centres in terms of care quality and patient outcomes.

Numerous academic papers have been published on outcomes in different subtypes of sarcoma and on centres’ measures to improve the quality of care. These efforts may originate in national legislation, as in Lithuania, which requires multidisciplinary teams to discuss all patient, and health centres to periodically publish their clinical outcomes online. Quality-improving measures may also be rooted in evaluation processes managed by organisations outside the country (e.g. the Organisation of European Cancer Institutes). However, Spain stands out for its well-established accreditation system, which ensures real clinical accountability for reference centres (see section 1.2). This system is mainly concerned with aspects related to quality (patient volume, existence of clinical protocols, etc.) and to a lesser extent with indirect care outcomes (e.g. time between diagnosis and treatment). Spain’s experience shows that accountability in terms of activities and outcomes has a major impact on the behaviour of teams and centres. However, it is challenging for the health authorities to periodically update the assessment criteria, as some become obsolete while others must be adapted to changing technologies and professional practices.

In France, the health authorities do not directly evaluate clinical outcomes. Rather, clinical networks indirectly fulfil this function for their members by means of the information system that they have. Maintained continuously, this information system allows the identification of gaps between centres (e.g. number of tumour board meetings). A recent article related to NETSARC’s activity showed that “the compliance to clinical practice guidelines and relapse-free survival of sarcoma patients are significantly better when the initial treatment is guided by a pre-therapeutic specialized multidisciplinary team” (Blay JY, Ann Oncol 2017).

Italy’s transition towards formalising its network of rare tumours, on this point, is the same as in the Spanish case. An MoH agency (AGENAS) supervises the data generated by different quality and outcomes indicators. Centres call for professionals to participate more closely in the definition of assessment criteria for the centres.

In other cases, the evaluation of clinical outcomes is restricted to the sphere of scientific societies, though with the advantage of having a fully functional National Cancer Registry (Finland, Czech Republic). The case of the Czech Republic is especially relevant due to the quality of available data – which show that patients treated in expert centres have better
survival outcomes than those in other hospitals – and because of the role played by the Czech Cancer Society in assessing the outcomes of different centres.

3.2 Patient association lobbies

The uncertainty that characterises the care journeys of patients with rare cancers has driven the work of patient associations as key actors in the generation of information resources and in political movements to improve access to expert centres. In Italy, for example, patient associations invest considerable efforts in political lobbying to promote patients’ access to expert centres, highlighting the dimension of healthcare migration and the high social costs that this phenomenon incurs for patients and families. Likewise, in the Czech Republic, patient associations have exercised considerable pressure to centralise treatments for paediatric cancers and rare adult cancers in expert centres, and they have also helped expert centres to be recognised as such at the national level.

In Spain, patients call for increased efforts to disseminate information among associations with regard to the existence and location of reference centres, as associations are often unaware of the status of different centres. In Finland and Lithuania, patients are present on ministerial commissions to define health system strategies on centralisation, financing systems, etc., and it is in this setting where they can articulate their priorities. In Finland, patients’ participation is even more visible because associations are integrated within the Cancer Society of Finland, an umbrella organisation that provides supportive and survivorship care, among other services and activities. Services like rehabilitation, information about coping with adverse effects of treatment, and counselling are all covered by social security and provided in a complementary way to hospital services. Finally, it’s worth noting the key role that patient organisations have had in France to promote the clinical networks that today are part of the institutional fabric of the health system.

3.3 Hospital financing

One element that emerged from the analysis in countries with an established system of expert centres for sarcoma, such as France and Spain, is related to the financing of reference centres. While their activities are reimbursed in some way by the system, the allocation of these funds is mixed in with hospital financing, so it does not have a direct impact on the services and professionals involved. In France, this issue is being gradually resolved.

Something similar occurred in Spain when, as was the case up to 2013, the MoH directly reimbursed care received in expert centres outside their region. This fund facilitated referral of patients between regions, but the money did not have an impact on the services because it was transferred to the regional treasury, or perhaps because it arrived only after some delay. The current situation, based on a direct compensation between regions, is unchanged on this point.

On the other hand, in the Czech Republic, one major problem that was identified was that the insurers operating in the country finance the diagnostic and treatment process for sarcoma in any hospital in the country, regardless of its degree of expertise. This undermines the ministerial decree recommending that these patients receive treatment in the 15 CCCs.
4. THE IMPACT FOR COUNTRIES OF ERNS INVOLVEMENT

4.1 Participating in the ERNs: expectations, potential benefits and possible barriers

The expectations on the impact that ERNs may have at a country level are the following:

- Contributing to give greater visibility to expert centres in rare cancers, by improving their standing at a national level as real reference centres.
- Helping to standardise clinical practice by identifying the specific recommendations or clinical practice guidelines that centres should follow, and by allowing reference centres to disseminate them throughout the country.
- Normalising online clinical consultations and holding virtual tumour board meetings, so that the supervision of the diagnosis and the treatment plan is centralised in reference centres, even if some services are delivered in hospitals nearer to patients’ homes.
- Improving the definition of expertise in the centres, as a given expert centre may exercise as such for one pathological subtype of sarcoma but not for another.
- Although officially the ERNs are concerned only with care objectives, various centres aspire for this structure to also facilitate exchanges in clinical research and achieve adequate patient volumes for certain subtypes that are very difficult to reach at a national level.

Potential benefits for participating centres:

- Discussing with “knowledgeable people” from specific areas of rare cancers (e.g. treatment options, analysis of pathological samples) and generating second opinions for patients. Advances in molecular profiling and the different degree of expertise in rare areas can be critical for decision-making with many patients.
- Formalising existing collaboration with other expert centres so that this is no longer an issue that depends strictly on professionals’ personal efforts.
- Connecting with the latest advances in the area of rare cancers, continuously receiving up-to-date clinical information.
- Being able to easily refer patients when necessary, albeit with the caveat that “our expectations regarding ERNs are expertise travelling rather than the patient”.
- Professional training and advancement, owing to normalised communication with other professionals sharing the same area of expertise in rare cancers. This implies exchanges of professionals between different European centres in the context of training programmes.

The following are some of the possible barriers resulting from ERN collaboration:

- Excessive workload, complicating the conditions for participating in the ERNs. Administrative support, data managers and financing for network meetings would facilitate the task of preparing information and collaborating.
- Interviewees hope that the e-health tool for exchanging and discussing medical records is user-friendly, avoiding duplications in the registry of information. Excessive
bureaucratization of the processes to request patient reviews could undermine professional motivation.
- Low level of English among some professionals, with the associated limitations in the communication of clinical cases.
- Lack of information on the objectives of EURACAN/ERNs. Many doctors do not know what ERNs are, so they should receive better explanations because involvement with EURACAN can contribute to improving rare cancer care in their countries.
- Not defining the role of the expert centres in the context of the ERNs. Giving medical advice, taking on cases for treatment, and including patients in clinical trials are all different objectives. Resource allocation should be aligned with the role that is defined.
- Not defining the role of non-expert centres in the context of the ERNs. It is relevant to establish a boundary around their care role for patients and in relation to ERNs, for example, establishing whether they can administer medical treatments. Their level of expertise for managing these patients should be evaluated, and based on the findings, the centres can serve a secondary role in the network or participate in a more limited way.
- While the patient volumes and standards of care required to participate in the ERNs are sensible, they block the systematic participation of Eastern European countries. This barrier could potentially be addressed by promoting the category of ERN affiliated centres.

4.2 Referring patients abroad: cross-border issues
How feasible is the normal referral of patients to other countries through the ERNs? The following three dimensions were highlighted when evaluating this possibility:

- **Administrative decision-making process.** International referral is currently a very complicated administrative and technical process due to the necessity to align the visions of expert clinicians and health authorities. International referral is not uncommon, but it does involve lengthy reimbursement procedures.

- **Patient acceptability difficulties.** Interviewees perceived that most patients would not accept travelling abroad to receive treatment due to language difficulties, reimbursement of travel expenses, the need for self-care, etc., but when this option could really benefit patients, clinicians should offer it to patients rather than deciding for them.

- **Different countries, different portfolios of services.** The list of approved drugs and their indications is not the same in all European countries, and the prices paid for a patient referred from another country are always set by the country where the treatment is delivered. This fact can cause significant problems and impede patient referrals that are justified on clinical grounds.
5. Conclusions

1) Singling out National Reference Centres (NRCs) across the six geographies tested requires these centres to play a leading role in the diagnostic-therapeutic processes of all rare cancer patients. Even though an informal reputation as a centre of excellence carries significant weight, health systems can be further strengthened in three ways: (1) awarding specific legal status or institutional recognition to expert centres; (2) targeting funding based on specialised services and units; and, (3) establishing a quality control and accreditation system to maintain accountability.

2) Officially appointing NRCs at a national level enables clinical expertise in rare cancers to be identified and benchmarked. The key components of this approach rely on: first, centralisation of clinical decision making to expert centres as well as clinical research and guidance on sources of critical evidence to be used. Second, a cooperation model that defines the relationships and communication methods between expert centres and other health providers, with a view to enabling agile clinical advice or patient referrals. Third, defining the expertise level of non-specialised centres as not all of them have the minimum expertise to coordinate with expert centres and provide treatments.

3) Equal access to quality care for sarcoma patients requires expert anatomopathology diagnosis from the outset. While accurate diagnosis is critical for patient treatment and prognosis, practitioners working outside expert centres must receive ongoing practical training to avoid taking needle biopsies. Enabling expert diagnosis is strongly recommended in health systems.

4) Planning of expert centres and medical services for rare cancers should be related to patient volumes while maintaining insight into pathology subtypes (e.g. bone sarcoma, retroperitoneal liposarcoma). There are various examples of health services reorganisation and sub-specialisation according to the different sarcoma subtypes. However this specialisation is often lost in the generic label of ‘reference centre’ or ‘university hospital’. Once clinical expertise is clearly signposted, at a sub-pathological level, all practitioners will be aware of where to refer specialist cases.

5) A network model, where patients are proactively coordinated and linked to long distance treatment via inter-hospital exchange, requires additional funding for NCRs. This extra funding would also support highly specialised services in NRCs such as molecular diagnosis, innovative and multi-modal treatments, which are more costly than the ‘standard care’ provided in non-specialised settings. Additional financing should be linked to the definition and assignation of NRC status.

6) Scientific societies and especially sarcoma groups should form a strategic part of the governance of highly specialised services for rare cancers whether it is intended to set up expert networks of NCRs. Selecting and evaluating medical centres against quality standards implies important costs in terms of knowledge management which may be tackled by health authorities in collaboration with expert professionals. However, creating a network of expert
centres requires linking the clinical decision-making frameworks to the needs for information sharing and knowledge transfer between expert practitioners (e.g. implementing a national tumour board on Ewing sarcoma). The different areas of expertise and therefore clinical roles of expert teams in the context of a network are inherent to a successful, formal network of expert centres.

7) The centralisation of patients in expert centres (or remote verification of clinical decision making), when coupled with clearly recognised NRCs, results in better access to expert advice and a well-organised sequencing of diagnosis-to-treatment process. Equity in access to quality care can also be considered in terms of clinical trials’ enrolment.

8) In addition to quality of care assessment, external evaluation of expert centres provides an important opportunity to benchmark quality of care and scientific research rather than patient volumes solely. In parallel, external evaluation can assist in standardizing care processes and structures across expert centres.

9) Health systems where expert centres lack specific status and a guidance role may limit the ERNs ability reach all patients across the country. Poor coordination at a national level has a European-wide impact as knowledge share and transfer is not ingrained across expert clinical environments. Moreover, a lack of nationally coordinated specialisation may create inequality for rare cancer patients, depending on where they are treated, which for many of them still means a non-expert centre close to home.
ANNEX 1. INTERVIEW QUESTIONS

**TOPIC 1. National reference centres (NRC): designation and role of national authorities**

1. Which are the processes leading to the designation of a NRC (e.g. for sarcoma) in your country? Is that a kind of accreditation process? Which are the conditions to be accomplished in order to be accredited? Which problems are intended to solve the official/formal designation of NRCs? Which was the previous situation?
2. Which is the specific embedment of NRCs within the national health system? Which elements of the national health system facilitate or hinder the development of NRCs?
3. When was this process established and for which cancers? How many centres do currently provide care for sarcoma? Is that a “closed” system right now?
4. Is that a model of “reference cancer centres” or “disease-reference centres”?
5. From a national perspective, is that a model of independent centres or rather a network of connected institutions?
6. What is and what should be the role of health authorities (e.g. stimulate collaboration, strengthen NRCs)? Do you (as a provider) feel “subject to” a shared system?

**TOPIC 2. National reference centres (NRC): clinical organisation**

7. Which are the implications for a given centre at being designated NRC in terms of clinical management, organisation and care delivery? All the patients are taking on by NRC or just selected cases?
8. Are there different “levels of complexity” (e.g. due to technology) between NRCs in your country?
9. Do clinicians from all NRCs use the same protocols/guidelines? If NOT, which ones do you use? If YES, is this body of knowledge built on their consensus? Is adherence assessed?
10. Are clinical outcomes assessed? How is quality of care assured? Is there a common accountability framework for all NRCs (i.e. control from health authorities on the basis of indicators, periodic assessment or database)?
11. Do the NRCs cooperate or exchange information at network level (at clinical or managerial level)? Which tools are being used (ICT, databases, etc.)?
12. Is clinical research being carried out in your centre? Do NRCs cooperate for clinical (e.g. RCTs) and/or outcomes research?
13. Are patients able to easily circulate between centres and NRCs and between NRCs? Are patients being supported?
14. According to your opinion, what is the degree of homogeneity in the quality of care offered by the NRCs?

**TOPIC 3: NRCs: connection with the European Reference Networks (ERNs)**

15. What is the current level of involvement of your centre in the ERNs?
16. What is the added value of ERNs respect to the national-based system? What is the potential of ERNs in improving cancer care?
17. What changes in your NRC do you expect from the involvement in the ERNs’ framework?
18. How the knowledge transfer is performed between national and European guidelines?
19. Which local factors can be identified as barriers or facilitators in the development of ERNs? In being involved in ERNs, do you feel that is your centre is losing autonomy? Do you think that ERNs are implemented through a win-win strategy?
20. Which lessons learned from the national experience can be useful for ERNs’ development and organisation?
21. What is/would be the contribution from your centre (or all national NRCs) to the ERNs?
ANNEX 2. PRACTICAL ASPECTS OF THE CASE-STUDY

- The Case-Study involves a process of research carried out at each country. The goal is to better know the organisation of rare cancer care at National level.

- As highlighted in the protocol the case-study focusses on sarcoma as example. This does not mean that information about other rare cancers is not relevant. What we intend is to use sarcoma to understand the impact of creating national centres for rare cancers.

- The case-study is not intended to describe how good or bad are the different experiences and neither to set a comparison between countries. The research is aimed at describing the process of creation of National-based centres for rare cancers and how they have been embedded in different health systems in Europe.

- We use the term “National centre for rare cancers”, but we are aware that the centres that have centralised the diagnosis and treatment of rare cancers are mostly third-level hospitals that deliver care for multiple diseases.

- Three inputs are of special importance and are expected to be delivered at each country:

<table>
<thead>
<tr>
<th>Inputs</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Regulation and policy framework of the National-based centres for rare cancers</td>
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<tr>
<td></td>
<td>Is there any regulation supporting the creation of National centres/hospitals for rare cancers? Please, let us know any legislation/regulation, administrative enactment, accreditation process, and/or any policy rules that were set up in order to create/organise the National centres for rare cancers. These documents might not be in English, so they can be delivered and described in the context of an interview during the on-site visit (see below).</td>
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<tr>
<td>2</td>
<td>Qualitative data based on semi-structured interviews (onsite visit)</td>
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|        | The core of the research is a 2-day onsite visit in which it is expected to interview key informants. The sample of informants will be the same at each country. We please ask for the following profiles: 

- 1, 2 or 3 policymakers from the Ministry of Health (and/or other health authorities) involved in the creation of national centres for rare cancers and with a view on European networks.

- 1, 2 or 3 clinical leaders in the field of sarcoma working at a national centre for rare cancers (they can be from different specialties). They will be asked about the relevance of having expert/s centre/s at national level, the clinical organisation of these centres and the involvement (actual or potential) in ERNs.

- 1, 2 or 3 hospital managers with expertise in clinical organisation and perspective on the transition towards the creation of centres for rare cancers at national level

- Optional: 1 patient organisation representative. We will try to select a patient through our partners Eurordis/ECPC, but if a patient is well-known and willing to participate, we would appreciate having the opportunity to interview him/her |

We are flexible with respect to the number of interviews; however, the sample should not exceed the 11-12 informants. As it is impossible for us organising an agenda including all these interviews, we would thank some coordination of the interviews to be carried out (some kind of schedule). Of course, the researcher can conduct the interviews in one place or moving to the designated locations.

The interview covers three topics related to National centres for rare cancers: 

1. designation and role of national authorities; 
2. clinical organisation of the centres (considering especially the situation of sarcoma); 
3. (potential) connection with ERNs

- The interviews are carried out with open questions, recorded (voice) and last for no more than 60min. We would adapt this time to the need of informants (30min, 45min...),
considering especially the time of clinicians.
- A sheet containing information about the study goals and a consent form will be handed out before starting.
- It is very important to involve participants with experience in the real life problems of this field.
- The researcher in charge (Joan Prades) has his expenses covered and travel arrangements will be made also by ours.

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<th>3</th>
<th>Clinical or process variables/indicators and patient information</th>
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|   | The third input considers those variables or indicators that are involved in the activity of national centres for rare cancers. Specifically, we would like to know (1-4):
|   | - “Are clinical and process outcomes of the rare cancer processes of care evaluated?” Please let us know the variables (clinical and process indicators) used to assess the activity on rare cancers (1).
|   | - “What information do circulates between a hospital and a national centre for rare cancer when a patient is referred?” Please let us know if there is any common procedure about the information to be delivered when referring a patient (diagnostic tests, patient information, etc.) (2)
|   | - “Was the diagnosis of a patient referred effectively a sarcoma?” Please let us know if you have any procedure or accountability mechanisms to verify that referrals made were appropriate (3).
|   | - “Is the patient satisfaction evaluated?” Please let us know if you evaluate patient satisfaction (4).

We do NOT ask for clinical results (quantitative data). The information required is only about the scheme of control and evaluation (indicators, variables) of rare cancers derived from the creation of specific centres. This information can be delivered and detailed to the researcher (Joan Prades) during the interviews.

- Once the completion of the research, all this information will be synthesised per country in order to “build” the case. We will send this preliminary synthesis to each country (before drafting the final report) in order to offer the possibility to propose changes about the contents.
- Please do not hesitate to ask for any additional information it might be needed. Thank you very much for your efforts.
ANNEX 3. INFORMATION SHEET

WP 10 – RARE CANCER POLICY

Nationally based centres for rare cancers: the background for European reference networks (ERNs)

There is broad consensus that networking is the most appropriate answer to the many issues pertaining to rare cancer care. The creation of European reference networks (ERNs) provides a clear window of opportunity to improve rare cancer care in Europe, potentially representing a comprehensive intervention across many different areas, including quality of care, research, education, prevention, diagnosis and treatment.

This study aims to provide an in-depth understanding of national experiences and their connection with the developing ERNs based on the perspective of physicians and clinical managers. They may gather relevant perspectives on how different European countries conceive and use the ERNs. According to the task 2.1 of the WP10, ERNs should be set into focus as the new framework for rare cancer care. However, taking into account their early stage of development, it was prioritized to approach “background” of ERNs (the National experiences) and its implications for them.

This study is ultimately intended to inform the debate among European cancer patients, scientific societies and representatives of cancer plans in order to generate recommendations on rare cancer care organisation at national level that could be relevant at the EU level. The study is not intended to describe how good or bad are the different experiences and neither to set a comparison between countries.

Main research questions

What are the relevant organisational and clinical management features at nationally based centres for rare cancers?

How have national reference centres been embedded in the health system? What lessons can be learnt from their implementation?

The national experiences selected for the case studies are: France; Spain; Italy; Lithuania; Czech Republic; and Finland.

Three inputs are of special importance and are expected to be delivered at each country:

1) Regulation and policy framework of the National-based centres for rare cancers
2) Qualitative data based on semi-structured interviews (onsite visit)
3) Clinical or process variables/indicators and patient information

Please, do not hesitate to ask for more information at jlprades@iconcologia.net or by accessing http://jointactionrarecancers.eu
ANNEX 3. CONSENT FORM

TITLE OF STUDY
Nationally based centres for rare cancers: the background for European reference networks

PRINCIPAL INVESTIGATOR
Joan Prades – Researcher on cancer care organisation and healthcare systems
Catalan Institute of Oncology (ICO) - 199-203 Gran Via de l’Hospitalet 08780
0034 636 857 873 - jlprades@iconcologia.net

PURPOSE OF STUDY
You are being asked to take part in a research study. Before you decide to participate in this study, it is important that you understand why the research is being done and what it will involve. Please read the following information carefully. Please ask the researcher if there is anything that is not clear or if you need more information. The purpose of this study is to analyse different nationally based hospitals for rare cancers in the context of their inclusion within the ERNs.

STUDY PROCEDURES
We adopted a case-study design based on the analysis of SIX nationally based centres for rare cancers. The national experiences selected as case studies are: France; Czech Republic; Spain; Italy; Lithuania; and Finland. The qualitative study consists of semi-structured interviews conducted during on-site visits.

VOLUNTARY PARTICIPATION
Your participation in this study is voluntary. It is up to you to decide whether or not to take part in this study. If you decide to take part in this study, you will be asked to sign this consent form. After you sign the consent form, you are still free to withdraw at any time and without giving a reason. Withdrawing from this study will not affect the relationship you have, if any, with the researcher. If you withdraw from the study before data collection is completed, your data will be returned to you or destroyed.

CONFIDENTIALITY
Your responses to this interview will be anonymous. Every effort will be made by the researcher to preserve your confidentiality. State measures taken to ensure confidentiality, will be: assigning code names/numbers for participants that will be used on all research notes and documents, and keeping notes, interview transcriptions, and any other identifying participant information in a locked file cabinet in the personal possession of the researcher.

CONTACT INFORMATION
If you have questions at any time about this study, or you experience adverse effects as the result of participating in this study, you may contact the researcher whose contact information is provided here.

CONSENT
I have read and I understand the provided information and have had the opportunity to ask questions. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and without cost. I understand that I will be given a copy of this consent form. I voluntarily agree to take part in this study.

Participant’s signature ______________________________ Date __________

Investigator’s signature _____________________________ Date __________