Deliverable 10:

Standard of care guidelines for VRT and very rare STS

Co-funded by
the Health Programme
of the European Union

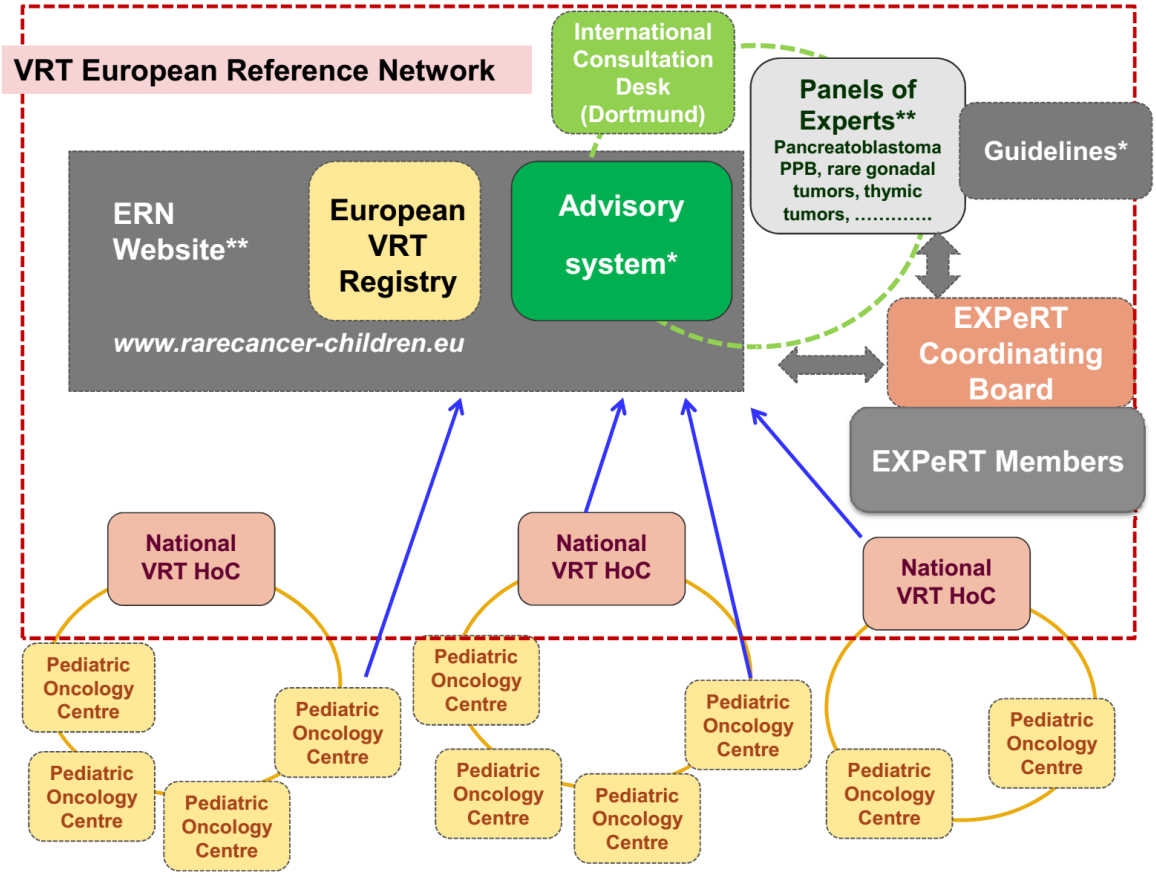
This publication arises from the project ExPO-r-Net which has received funding from the European Union in the framework of the Health Programme (2008-2013), grant agreement nr. 2013 12 07. The content represents the views of the author and is his sole responsibility and it can in no way be taken to reflect the views of European Union bodies. The European Commission and/or Chafea do not accept responsibility for any use that may be made of the information it contains.

ExPO-r-NeT – European Expert Paediatric Oncology Reference Network for Diagnostics and Treatment

WP8 - Integrating children with very rare tumors in a European Reference Network

The deliverables provide in WP8 were the preparation of standard of care guidelines for some pediatric very rare tumor including some rare soft tissue sarcoma.
During the development of the project it became clear that deliverable and milestones included in the projects had to be considered as part of an integrated system dedicated to children and adolescents with VRT.
A reference network model has been elaborated (see figure 1). The parts with the asterisk have been realized as deliverable (*) or milestones (**) during EXPO-r-Net.

Figure 1.



The realization of the Advisory system, that now rely on a virtual case consultation platform internet based, represents an additional, major, deliverable produced by this WP.

1) Standard of care guidelines for VRT and very rare STS

Pediatric very rare tumors (VRT) constitute an extremely heterogeneous group of neoplasms. Some of them are typical of pediatric age, while other more commonly arise during adulthood and only rarely develop in children. Using the definition *any solid malignancy or borderline tumour characterised by an annual incidence < 2/million children <18 years old and/or not already considered in other clinical trials* the European Cooperative Study group for Pediatric Rare Tumors (EXPeRT) has identified a number of pediatric VRT (see table 1). Due to the low number of patients it is very difficult – or even impossible - to conduct clinical trials on them, and this makes it hard to arrive to evidence-based treatment guidelines. As a consequence, the treatment of patient with VRT is often individualized.
The same situation is evident for rare pediatric soft tissue sarcomas (STS). In fact over the past 40 years patients with the most frequent hystotypes such as rhabdomyosarcoma or synovial sarcoma have been enrolled in national or international protocols and the chance of cure for these patients has progressively increased. The same did not occur for children with very rare sarcomas because their limited numbers.
Therefore there is a need for international recognized recommendations for the diagnosis and treatment of pediatric VRT and rare STS.

Methodology

The first step was the involvement of the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) and the European paediatric Soft tissue sarcoma Study Group (EpSSG), the largest European Research Groups working on pediatric VRT and STS, respectively.

The process to elaborate internationally shared recommendations included:
- Identification of the tumor of interest on the base of its relevance, and previous EXPeRT/EpSSG experience (i.e. data analysis and publication).
- Designation of two coordinators for each VRT/STS on the basis of their experience (data analysis, publications, personal experience).

Coordinators have to
- search the medical literature and select the relevant papers
- propose a series of recommendation in a form of a first draft of recommendations
- identify the main diagnostic and therapeutic problems for the designated VRT/STS. The first draft has been circulated, along with the relevant publications, to all member of EXPeRT/EpSSG.

A second draft of recommendations has been produced taking into account proposals from EXPeRT/EpSSG.
This second draft has proposed to external experts identified by the coordinators on the basis of a recognized experience. A third draft has then be produced and circulated to a larger group of people with experience on the identified tumor.

A fourth draft has been created and finally discussed and approved at an international consensus conference that has been held the 29-20 of March 2017, in Padova.

The "strength" of recommendations has been categorized:

- Highly recommended (HR): 95% of experts agree
- Recommended (R): at least 80% of experts agree
- Possible (P): 60 to 80% of experts agree
- Agreement not possible (ANP): less than 60%

Even with the difficulties posed by the rarity of this tumors and the limited number of scientific report available, the above described procedure is in line with the requirements of U.S. Institute of Medecine for recognizing credible guidelines.

1. Has an explicit description of development and funding processes that is publicly accessible
2. Follows a transparent process that minimizes bias, distortion, and conflicts of interest
3. Is developed by a multidisciplinary panel comprising clinicians, methodological experts, and representatives, including a patient or consumer, of populations expected to be affected by the guideline
4. Uses rigorous systematic evidence review and considers quality, quantity, and consistency of the aggregate of available evidence
5. Summarizes evidence (and evidentiary gaps) about potential benefits and harms relevant to each recommendation
6. Explains the parts that values, opinion, theory, and clinical experience play in deriving recommendations
7. Provides a rating of the level of confidence in the evidence underpinning each recommendation and a rating of the strength of each recommendation
8. Undergoes extensive external review that includes an open period for public comment
9. Has a mechanism for revision when new evidence becomes available

All this requirements have been satisfied apart from number 4, due to the limited quality and quantity of available evidence. There is concern regarding point 9 because the regularly update of recommendations in the long term may be compromise by the lack of funding now that the EXPO-r-NeT project is finished.

Identification of VRT and rare STS

After discussion with EXPeRT and EpSSG Board members a priority list of VRT and rare STS has been established and two coordinators identified:

1) Pleuropulmonary Blastoma (coordinators: D. Orbach, G. Bisogno)
2) Pancreatoblastoma (coordinators: E. Bien, A. Ferrari)
3) Sex cord stromal tumors (coordinators: D. Schneider, G. Cecchetto)
4) Infantile Fibrosarcoma (coordinators: D. Orbach, A. Ferrari)
5) Alveolar Soft Part Sarcoma (coordinators: D. Orbach, A. Ferrari)

Priority was established on the basis of the absence of standard guidelines and the unique experience gathered by EXPeRT and EpSSG in these years on these specific tumors.
The decision was to start with Pleuropulmonary Blastoma to establish a working method and create a recommendation template that could be used for the other tumors.

Standard of care guidelines dissemination

Beside the international consensus workshop held on March 2017 the final documents have been presented at the EXPeRT and EpSSG meetings and are available in EXPORNET, EXPeRT and EpSSG websites.

To give a wider publicity to the documents prepared we have approached the editor of a peer-reviewed journal that has declared his interest for the publication of the document in a special series.

Standard of care guidelines as part of a European reference network

The documents elaborated have not been thought as a standalone documents but represent an essential part of the network developed during the EXPO-r-NeT project (see figure 1).
In fact standard recommendations will be used to support the Panels of Expert in their advisory activity.
On the other hand the experience that we hope to collect through the advisory system we have set up and its database will help to update and modify (if needed) the recommendations.

The standard of care guidelines that have been elaborated, discussed and widely accepted are attached.

2) Advisory system for Very rare tumors: the VRT-VTB project

The introduction of multidisciplinary treatment strategies constitutes a major advance to the improvement of survival of children with cancer. For more common childhood cancers, multimodal treatment is centrally coordinated by national or multinational cooperative groups and reference centers. Thus, an optimized orchestration of different therapeutic modalities is achieved with the best possible and risk adapted stratification, scheduling and dosing. In addition, patients with particularly problematic cancers can be referred to experts, both for consultation and for treatment.
Most cooperative groups and reference centers offer medical/treatment guidelines to the collaborating centres, that address these highly specific questions. Central review of pathologic diagnosis is often offered and, in some instances , multidisciplinary evaluation of difficult cases is provided. This consulting activity is organized in different ways and may provide different levels of assistance depending on available local resources and organization. In some, but not all of these activities, the consultation takes place within an interdisciplinary tumour board orchestrated by the responsible study coordinators.
Based on these experiences the constitution of officially recognized well organized tumour boards is considered an essential component of excellence in paediatric cancer care, as they may coordinate a broad range of medical experts in different disciplines, allowing for discussions and decisions on how to best care for each single patient with cancer and thereby assuring quality of care.
While such initiatives have already been established for more common childhood cancers, such infrastructure is unavailable for very rare paediatric tumours (VRT). In total numbers, all paediatric cancers might be considered “rare”. However, in the “uncommon” rare paediatric tumours, the problems are not only infrequent events but the complexity and heterogeneity of diagnoses. Indeed, the panel of diagnoses may include adult cancers, such as epithelial cancers, that rarely occur in the pediatric age (e.g. colon carcinoma, adenocarcinoma, melanoma etc.), and specific pediatric entities with extremely low incidence (e.g. pancreatoblastoma, pleuropulmonary blastoma etc.). As a result, histopathological diagnosis may be uncertain and too unspecific, and the responsible physicians at a clinical center may never have treated a patient with this particular diagnosis before. Sometimes, it may also be difficult to find an expert on a particularly rare tumour - even on a national basis. The extreme rarity of these diagnoses also leads to the obvious lack of scientific evidence with regard to optimal treatment.
Thus, the experience in the management of VRT is low and may impact the quality of care in these patients, too. In contrast to more frequent tumour entities, no national study centers with the appropriate infrastructure have been established, and the visibility of very rare tumour study groups may be less compared to study groups of more common paediatric tumours.

Central consultation at reference centers is of critical importance for the care of patients with very rare cancers, and even more than for more frequent cancer types, in which clinical experience is more widespread.
Therefore, the establishment of a central virtual tumour board (VTB) is essential to create a network of experts in different tumours that can discuss the best management

of patients with VRT. This VTB has to be established in an international setting that includes experts with outstanding expertise. Recent advances in telecommunication, such as modern broadband telemedicine technology, have made possible the establishment of such tumour boards. These technologies can overcome physical limits and may connect teams of specialists from different centers and even different nations or continents in a VTB.
This VTB can be contacted for requests regarding verification of diagnosis and optimal treatment (see the attached consultations request sheet). To ensure high quality of consultation, standard requirements for clinical consultation will be established, including pathology and surgical reports, imaging and clinical documentation.
The discussion, decision and clinical data on treatment and outcome will be documented centrally. Lastly, a tracking system for follow-up of each patient will be included, allowing for expanding the knowledge of outcomes in these rare tumours. Thus, a central VTB may become a formidable consultation platform to increase the experience of the experts and transfer knowledge to the paediatric oncology community.
The implementation of VTB has also been included in the EU Directive 2011/24/EU of patients' rights in cross-border healthcare as a tool to increase the capacity of healthcare providers and fundamental to create European Network of references.
VTB can provide medical advice, allowing the patient to receive appropriate treatment in the local Centre, but can also facilitate access to Centres with adequate expertise throughout Europe if a particular treatment is needed.

During the last decade, several national groups have been established that specifically focus on VRT in children and adolescents. These initiatives have increased the awareness of the problem of VRT. In June 2008 this led to the formation of a new cooperative group, European Cooperative Study Group for Pediatric Rare Tumours (EXPeRT). The primary aim of this group is to empower the clinical and biological research on VRT by promoting collaboration between the founder national groups: Italy, France, United Kingdom, Poland and Germany. It is expected that additional European countries will join the group in the short term.
The establishment of a VRT-VTB is supported by the experience gained by EXPeRT in the recent years and would represent an important step in the further development of EXPeRT activities. The establishment of the VRT-VTB in coordination with other EXPeRT activities will also provide a framework and possibly human resources to sustain this initiative after the conclusion of ExPO-r-NetT.

1 Aims

To establish a virtual tumour board (VTB) dedicated to very rare cancers in the paediatric age (0-18 years) accessible to paediatric oncologists in all EU member states.

To define the structure and the organization of the VTB.

To define standard operative procedures (SOPs) for inquiries and responses to clinical questions.

To build a database of experience based on cases discussed through the VTB.

2 Expected results

The establishment of a well-organized VRT-VTB will allow physicians to:

- discuss cases with worldwide and multidisciplinary experts
- explore various diagnostic/therapeutic options, even if they are not available in the center caring for the patient
- increase experts' experience thanks to their exposure to a larger number of cases
- continuously expand and refine knowledge on rare tumours

and patients to:

- benefit from the collective international experience of several specialists
- have access to modern treatments
- receive treatment locally but based upon international advice and supervision
- be referred to a different center if particular treatment is needed and not available locally
- avoid extensive and often misguided search and travel to find the "right" person and the "best" center

3 Project coordination

The project will be coordinated by the ExPO-r-NeT WP8 associated members:
Gianni Bisogno, University Hospital of Padova, Italy
Andrea Ferrari, Istituto Nazionale Tumori Milano, Italy
Dominik Schneider, Klinikum Dortmund, Germany

They are in charge of overseeing the complete process and in particular defining the structure and working procedures of the VTB.
This document will be reviewed by the members of the EXPeRT and external reviewers for suggestions and approval.

4 VTB structure

EXPeRT Tumour Board

At least three international experts will be identified for each VRT entity.
Experts can be identified by the project coordinators and/or proposed by the national coordinator of the European Cooperative Groups dedicated to VRT.
Experts should have documented experience with the indicated VRT and produce documentation of that, e.g. by sending a CV with pertinent studies and publications to the VTB desk/project coordinators.
They should also confirm their interest, duty and availability to act as international expert.
If they fail to respond to the advisory requests for one year in a timely manner, without good reasons, another expert will replace them.

ADVISORY DESK

A central Advisory Desk (AD) has been created in Dortmund
Tel: +49-231-953 21680
Email: expert-advice@klinikumdo.de

A desk officer/manager/coordinator has been identified to run all the activities of the advisory desk that will include:

a) managing the advice requests
- receiving the request (e.g. attached request form)
- assuring that all the necessary information for a complete case description are provided by the requesting center, including pathology, radiology and surgical reports
- sending the information to the dedicated international experts
- receiving the international expert advice
- sending the advice to the requesting center and the national coordinator

b) managing the advisory data base

c) managing the VTB system

d) produce an annual report of the advisory activities

The Advisory desk will also be in charge of possible administrative and organizational aspects concerning the advisory activity.

ADVISORY DATABASE

A database will be created to collect all the information necessary to provide advice. The database will also contain the decision taken by the national center and will continuously include the patients' follow up. This is important to monitor the effect of advice and learn from experience.

NATIONAL COORDINATOR

Paediatric oncology centres may ask advice directly to the VRT-VTB.
However in countries where a national group dedicated to children with VRT exists we strongly encourage that request will be sent through the national coordinator of the national VRT group for paediatric VRT. This could avoid to submit queries that can be solved on a national level. In addition, the coordinator may assist in overcoming language barriers e.g. in the evaluation of source data.
We will try to identify a colleague that can act as national contact for countries where a national VRT group does not exist.

A person will be required to act as coordinator/national contact of the VRT activities in each European country. The national cooperative group dedicated to VRT will designate him/her.
In those countries, where such a group does not exist, the national paediatric oncology society chair will be contacted and asked to designate an appropriate person.

The national coordinator/national contact's role is:
- to organize advice on a national level
- to receive and manage the request of advice from the national centers
- to provide advice consulting with experts on a national level, including assurance of correct diagnosis and staging of the tumour
- to ask for international advice if the experience on a national level is considered not enough
- to assure that all the relevant information are provided by the national center to obtain international advice
- to act as an intermediate between the international advisory desk and the centers asking for advice.

5 Advisory procedure

Requests for advice
The VTB will accept requests from the physician who is responsible for the patient's care or from the VRT national coordinator. The physician will go through an identification procedure.
Parents, patients or other not professionals are not allowed to ask for advice and will be invited to submit their requests, however, through the responsible physician. This restriction is required in order to assure reliable source data and meaningful consultations processes.
Request concerning more frequent tumours will not be considered, as well as general request of information or help.

Requests could be send in two ways
1) using a form that has been prepared (see appendix 1) – and will continuously be updated - detailing the minimum information requested for advice. All requested information must be sent to the Advisory Desk (expert-advice@klinikumdo.de)

2) Using a virtual consultation system (VCS) internet based that allow to send patients information and upload reports and images (http://www.raretumors-children.eu/)

   Material has to be submitted, exclusively in English language:

- Application of the medical doctor seeking advice, including question of consultation, and confirmation that the patient has agreed for the transfer of clinical data
- Clinical summary, including diagnosis, staging and course of treatment
- Surgical records
- Histology review, including central review at the national pathology reference center, if available
- Radiology report (ideally full radiology investigations should be submitted)
- The patient's responsible doctor should also confirm the patient's/legal guardians consent for further request, including follow up update, that may be formulated by the Advisory Desk
- All materials should be anonymized before being sent to the advisory desk

Management of advice request
The Advisory desk manager will check for the completeness of information, asking for missing information if this will be the case.
All the information will be circulated to the experts previously identified for each specific VRT.
The information will be also sent to a larger contingent of EXPeRT to enlarge the possibility of getting advice. Collaboration with North American experts is also possible and foreseen in the future.
The Advisory desk manager will inform the national coordinator of the request if the request has not arrived through him/her.

Delivery of Expert Advice
One of the experts will be responsible to write the advice letter, taking into consideration all the opinions received.
The Advisory desk manager will send the international advice letter to the national coordinator and the physician in charge.

All this process will be managed through the advisory desk.

6 Advice evaluation

The advisory procedure should also include indicators of the quality of the process and utility for requesting physician. This will include questionnaire and patients follow up forms

7 Informed consent

The request of advice to the VRT board must be sent after written informed consent has been obtained from the patient, parent or legal guardian.
The request of consent is left to the treating physician in agreement with the local rule.

The treating physician will confirm in the consultation form that the patient/legal tutor has been informed about the advice request and have agreed on the procedure including the possibility for the Advisory Desk to store data, ask further data including follow up information and use data for future consultation and analysis.

8 VRT Virtual Consultation system

Telemedicine technology is an attractive tool for international tumour board. An effective consultation system must however take into account for the different resources available in different countries.
Email, fax, post seems easily accessible in all European countries and will be used to circulate information.
An internet web-based consultation platform to exchange data safely and effectively will be also implemented.
This platform will serve also database to collect experience.

In a later phase of the project each affiliated site participating in the VTB should be equipped with advanced videoconferencing equipment, that projects the presenting physician's image and voice, along with detailed images of a patient's pathology slides or radiological scans. The high-definition images and sound run through encrypted Web-based technology, ensuring both maximum security and optimum quality.
The responsible physician may be included in the discussion as a guest. The physician may thus present the patient and discuss therapeutic options that are available at the local treatment centre.

The development and utilization of these tools strongly depend on the human and economic resources that will be available.

9 Compensation

Resources in term of time and funding are major limitations to the optimal development of the advisory process. Expert physicians, usually very busy with their own patients, must have time to carefully review all the material sent, discuss and prepare common recommendations.
Advice often must be given in a timely manner to be of help for a patient in a difficult and sometimes life-threatening condition, due to the tumour.
The structure to assure that the process develops in a coordinated, effective and expeditious way requires personnel and tools that local hospitals have no means to support.
Ultimately the goal should be that this consultation process in the VTB shall be reimbursed by the National Health System and/or the medical insurance of the patient according to the organization in the different Member States.
It is important to underline that resources dedicated to the VRT-VTB will, in the medium-long term, contribute to significant savings in terms of improved patient care, reduction of patients' migration and optimal use of available resources.

10 Legal aspects

The final responsibility decision on how to treat the patients will remain with the responsible physician in charge of the patient. This will be made clear when the advice will be requested and written in the international advice letter.

11 VRT-VTB Project Achievements

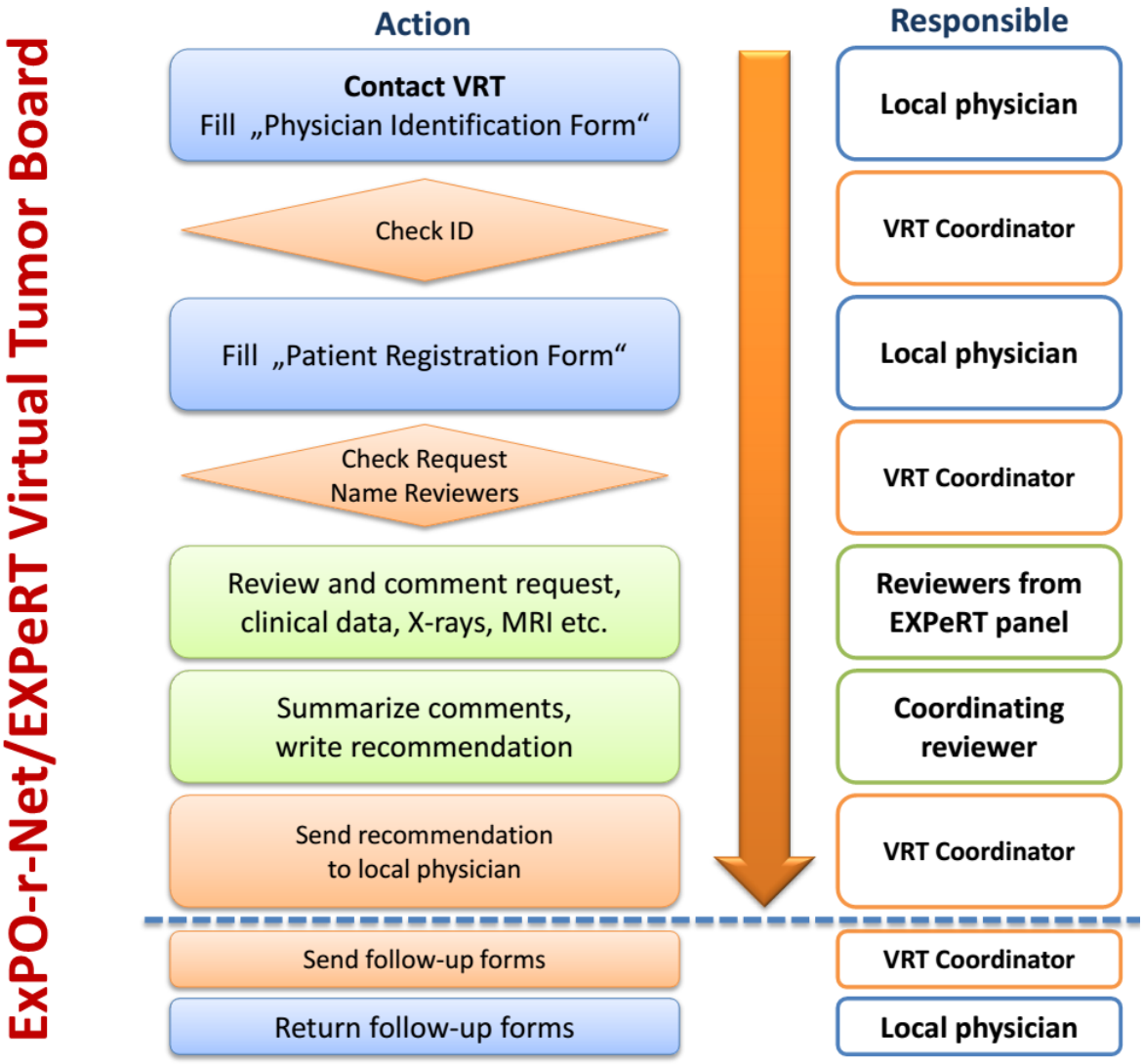
During EXPO-r-Net we developed the two form of activities included in this project

A pilot phase based on forms (often sent by email) has been carried out from October 2014 to February 2015 (see Ped Blood Cancer vol 62, S353, 2015). This type of activity is still through the advisory desk located in Dortmund and has been extremely important to gather information to built a virtual consultation system

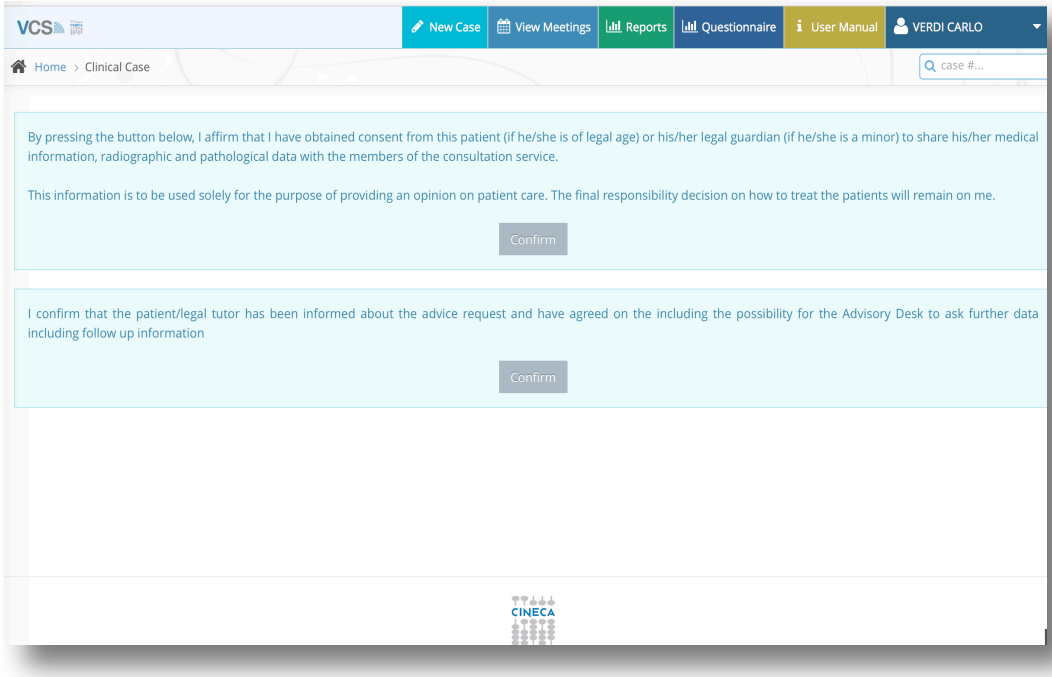
With the technical support of CINECA, the virtual consultation platform internet based has been realized and can be accessed through the rare tumors website: http:/vrt.cineca.it.
The virtual case consultation system opened the 23th of May 2017, and the first case entered from Denmark.

The virtual cosultation system data flow and some slides taken from the test website of the virtual consultation system are reported below

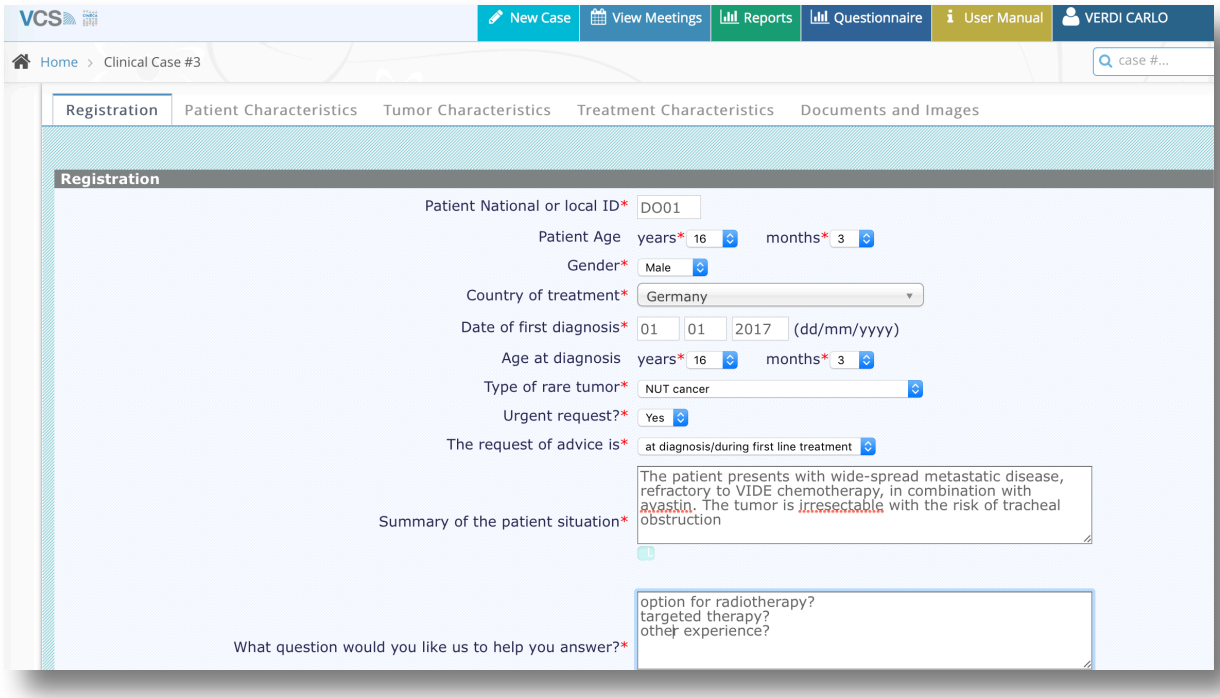
VRT Virtual Consultation System: Action and responsibilities



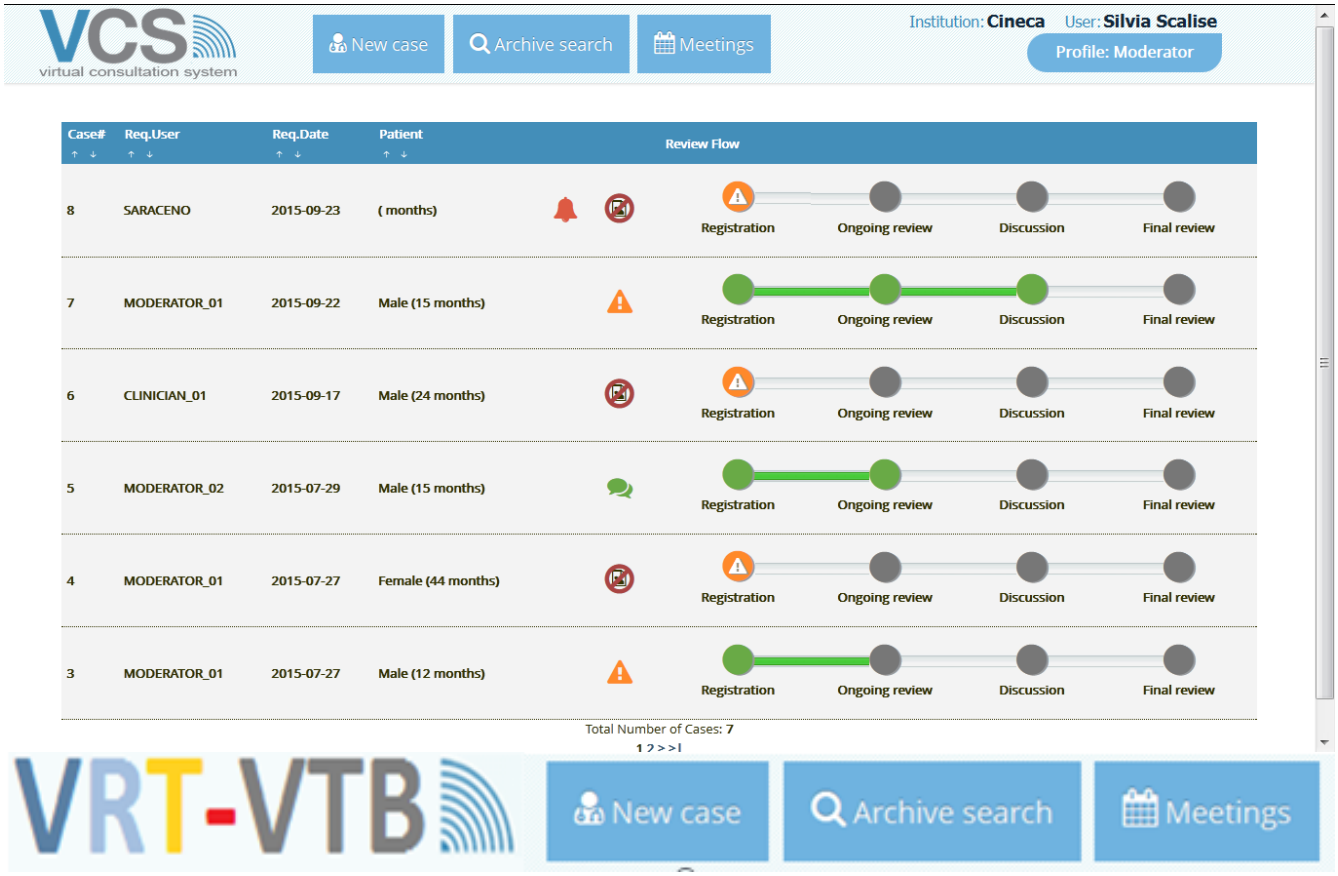
A) Registration of the patient responsible clinician



B) Patient data



C) Case list


VCS
virtual consultation system
New case
Archive search
Meetings
Institution: Cineca
User: Silvia Scalise
Profile: Moderator
Case#
Req.User
Req.Date
Patient
Review Flow
8 SARACENO 2015-09-23 (months)
7 MODERATOR_01 2015-09-22 Male (15 months)
6 CLINICIAN_01 2015-09-17 Male (24 months)
5 MODERATOR_02 2015-07-29 Male (15 months)
4 MODERATOR_01 2015-07-27 Female (44 months)
3 MODERATOR_01 2015-07-27 Male (12 months)
Registration
Ongoing review
Discussion
Final review
Total Number of Cases: 7
1 2 >> I

VRT-VTB
New case
Archive search
Meetings

VRT Virtual Consultation System: Action and responsibilities