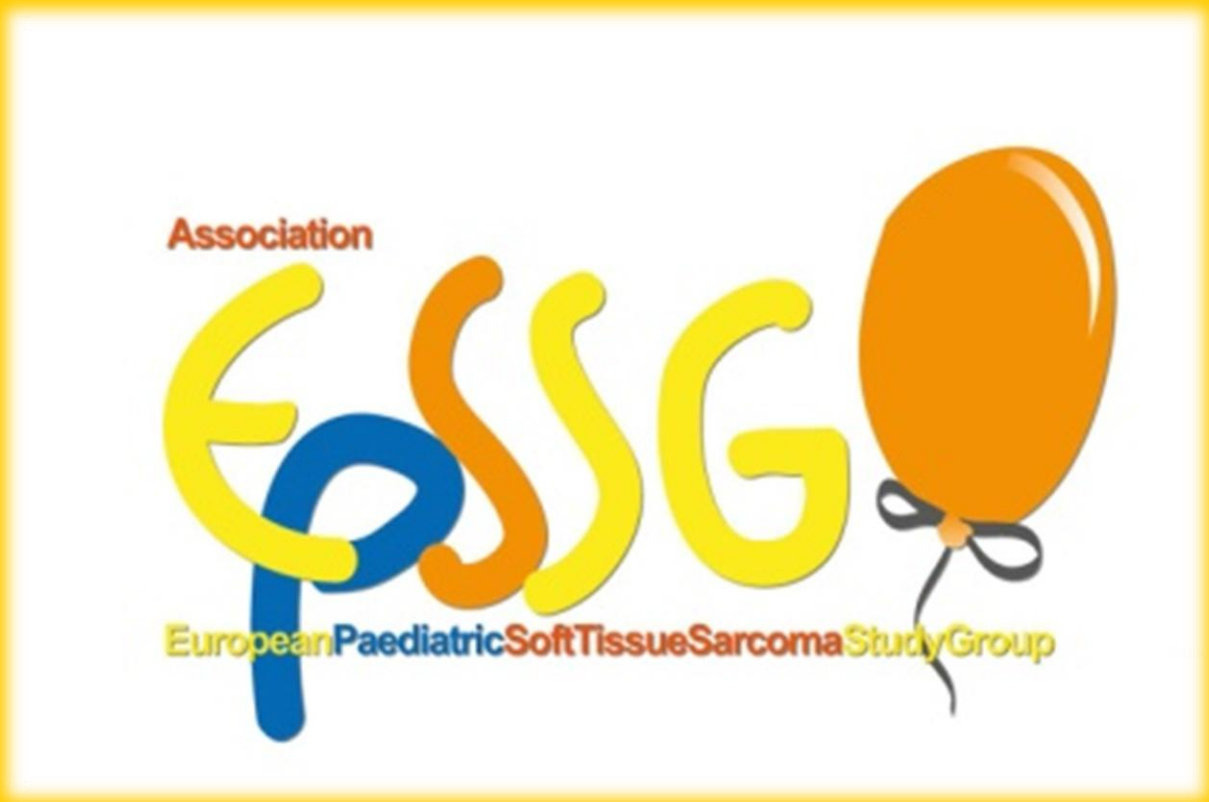
ANNUAL REPORT 2021



EPSSG ASSOCIATION

The European Paediatric Soft tissue sarcoma Study Group

IN MEMORY OF MODESTO (TINO) CARLI (1941-2021)

It is with great sadness that we inform the pediatric oncology community that Tino Carli passed away on 23 March.

Modesto Ottaviano Carli was born on July 1941 in Asiago, a small town on the mountains of the Veneto Region in the northeast of Italy. Asiago always remained in his heart as his hometown and a special place where he could ski, do long walks, and meet old friends. Modesto's father was an engineer and fought in the "Resistance" against fascism during the second world war. He was killed when Modesto was 4 years old. After the war, his mother became a member of the Italian Parliament. She raised Modesto, and his brother Alessandro, with a positive attitude towards life despite the suffering the family had gone through.

Modesto moved to Padova, where he studied, graduated in medicine in 1968, and became a pediatrician in 1970. He had a successful academic career, becoming a full professor in 2002 and Director of the Pediatric Hematology-Oncology Division of Padova in 2005. In Padova, he also met his beloved wife Bianca (Biki).

As a young doctor, he went to Paris (at the Institut Gustave Roussy under Dr. Schweisguth, 1973 and 1975) and the USA (St Jude Children's Research Hospital, 1977). In Paris, he heard children's voices and crying coming from a hidden ward, he entered and discovered that leukemia was only one of the malignancies that killed children in those times.

From that moment he devoted his life to care for children with solid tumors and to research into new treatments. Right from the beginning, he believed in team working and promoted national and international collaboration. In 1979 he launched the first Italian protocol for children with rhabdomyosarcoma and founded the Italian Cooperative Group with the support of Vito Ninfo, Guido Sotti and Maurizio Guglielmi (all pioneers in pathology, pediatric radiotherapy and surgery). Since then, every year, all Italian pediatric oncology working groups have gathered in Padova once a year to discuss, present ideas, and share information and friendship.

In the eighties, he started to collaborate with other cooperative Groups in Europe (as a good friend of Jorn Treuner, Francoise Flamant, and later Odile Oberlin, Michael Stevens, Ewa Koscielniak) and the Intergroup Rhabdomyosarcoma Study group (and later COG) in the United States (Harold Maurer, Beverly Raney, Jim Anderson, and Doug Hawkins among others). Money to support networking activity and travelling was always limited, so we often shared hotel rooms and "networking" dinners were in our private houses thanks to the help of our wives (luckily everyone was happy to come to Padova). He was at the core of the formation and funding of the European paediatric Soft tissue Study Group (EpSSG), and he was designated as its first Chair when the EpSSG Association was formally established on the 7th December 2011 at Palazzo del Bo', the historical site of the University of Padova.

He was elected president of the Associazione Italiana di Oncologia Pediatrica (AIOP) in 1994. He was a strong supporter of SIOP, presenting at many meetings, and proud to have been the organizer of the XVII SIOP Annual meeting in Venice, in the memorable Scuola Grande di San Rocco. Tino loved remembering these pioneering times: he had to clean the meeting room by himself the day before the Congress to save money.

With all the ups and downs of human life, Tino was a happy pediatric oncologist. He was happy in his job and proud of what he knew and achieved in the service of children and their families. Away from work, he enjoyed being active: racing on his beloved bicycle, skiing, and walking in the mountains. He was proud of the success of his ever welcoming family, from his wife Biki who sadly pre deceased him, to the children Giovanni, Chiara and Paolo, and his grandsons.

'**When someone is happy in life, they give more freely to others**'. This is what Tino did with his patients and their families, his friends and his colleagues. His generosity and collaborative spirit is the legacy he leaves for us all.

THE EPSSG ASSOCIATION

The European Paediatric Soft tissue sarcoma Study Group (EpSSG) is an international organisation for professionals devoted to the care and treatment of children and young people with cancers known as soft tissue sarcoma (STS). This includes the most common STS, rhabdomyosarcoma (RMS), and a wide range of other cancers known collectively, as Non Rhabdomyosarcoma Soft Tissue Sarcomas (NRSTS).

The legal entity for EpSSG activities is the EpSSG Association. This exists to promote and manage clinical trials, encourage and facilitate clinical and basic science research, foster optimal standards of care, organise educational meetings for its members and other professionals, and advocate for patients with STS.

It collaborates with other similar groups in Europe, North America and elsewhere.

EpSSG has its administrative and legal home in Padua, Italy. An elected board manages it, and its membership is open, by application, to professionals who have an interest in the research or treatment of these diseases when they occur in children, teenagers and young adults.

This report summarises the main EpSSG activities for 2021. Importantly, we have had the opportunity since 2016, to welcome parents of sarcoma patients to collaborate with us and support the development of our activities.

Further information is available on the EpSSG website: www.epssgassociation.it

EPSSG BOARD

Dr. Hans Merks	•Chairman - Utrecht, The Netherlands
Dr. Andrea Ferrari	•Treasurer, Milano, Italy
Dr. Veronique Minard-Colin	•Paris, France
Dr. Michela Casanova	•Milan, Italy
Dr. Henry Mandeville	•Sutton, UK
Dr. Timothy Rogers	•Bristol, UK
Dr. Gabriela Guillén Burrieza	•Barcelona, Spain
Dr. Nadège Corradini	•Lyon, France
Dr. Lisa Hjalgrim	•Copenhagen, Denmark

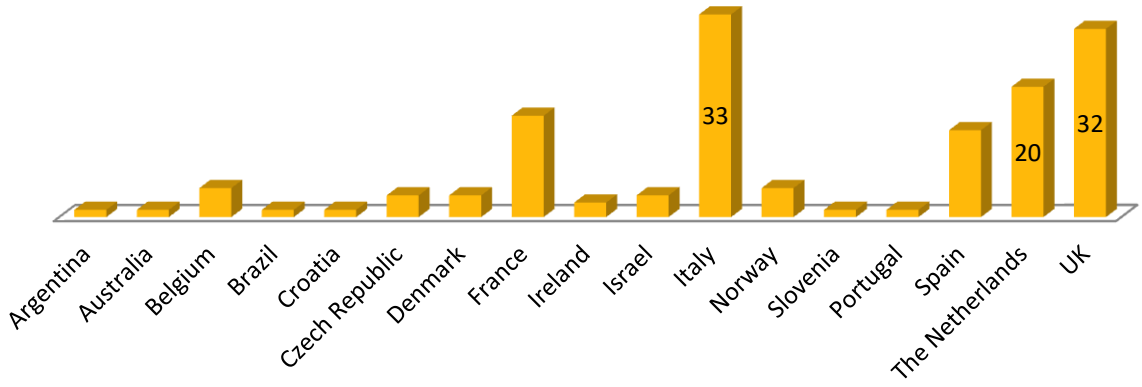
Board meetings were all held virtually on the following dates in 2021 due to the pandemic emergency: February 1st, April 6th, May 3rd, June 7th, July 6th, September 13th and November 8th. The board has organized meetings with Discipline Panel Committees in order to be updated on the work of Committees. In particular the meetings were held in March 1st and in October 15th.

The EpSSG 2021 Spring meeting was held within the SIOP Europe 2021 2nd Annual Meeting 29-30th of April. We had business meetings and joint meetings with other working groups. The EpSSG 2021 Winter meeting was organized virtually with the help of Bambino Gesù Hospital, Rome in December 2-3, 2021.

EPSSG MEMBERSHIP

EpSSG studies are undertaken in the following countries: Italy, France, UK, The Netherlands, Spain, Portugal, Belgium, Ireland, Denmark, Norway, Czech Republic, Croatia, Slovenia, Israel, Argentina, Brazil, Greece, Australia and New Zealand**.** In 2021, there were 144 individual members of the EpSSG from 20 different countries. These two years we welcomed new members from Portugal, Switzerland and Greece.

EpSSG members 144



EpSSG Subcommittees

	Chair
Biology	Prof. Beat Schaefer, Zürich, Switzerland
Pathology	Dr. Rita Alaggio, Rome, Italy
Radiology	Prof. Rick R. van Rijn, Amsterdam, The Netherlands
Surgery	Dr. Sheila Terwisscha van Scheltinga, Utrecht, The Netherlands
Radiotherapy	Dr. Raquel Davila Fajardo, Utrecht, The Netherlands
Phase I/II trials	Dr. Susanne Gatz, Birmingham, UK

EpSSG Meetings 2021

The Spring meeting in 2021 was organized virtually because of the COVID Pandemic during the 2nd Annual Meeting of SIOP Europe. In particular EpSSG had joint meetings with ExPERT group, Cooperative Weichteilsarkom Study (CWS-german group) and the Innovative Therapies for Children with Cancer in Europe (ITCC group).

In addition, we had a very successful EpSSG Winter meeting which took place on 2nd and 3rd of December, 2021 supported by Bambino Gesù Hospital Rome. It was hosted by Dr. Giuseppe Maria Milano. During this meeting we had outstanding presentations from clinicians, biologists and parents.

The discipline panel groups for biology, radiotherapy, NRSTS TMC, surgery, pathology, phase I/II, and radiology, met separately in the week leading to the main meeting.

This 'virtual' format has become a new way of disseminating the knowledge and maintaining close working-relationships within our association and delivered an interesting meeting that welcomed 118 participants.

THE NEW FRONTLINE AND RELAPSE STUDY IN RHABDOMYOSARCOMA

(BY PROF. MERIEL JENNEY AND DR. JULIA CHISHOLM)

The FaR-RMS Trial – Trial Update February 2022

An overarching study for children and adults with Frontline and Relapsed RhabdoMyoSarcoma

The FaR-RMS trial is an overarching trial for all patients with newly diagnosed and relapsed paediatric-type rhabdomyosarcoma and is open to patients of all ages. The trial has an innovative multi-arm, multi-stage design that allows the testing of new combinations of therapy in upfront and relapsed settings in phase Ib, phase II and phase III.

The trial has now been open for over a year. It is recruiting well and we are pleased to announce the imminent opening of the newly developed relapse research question, funded by Bayer.

We are delighted that there is wide international interest, and that in the last year, several countries new countries have expressed interest in opening the trial and have begun the set-up process. The current recruiting countries are:

Australia (6 sites open)

Denmark (2 sites open)

Greece (7 sites open)

Israel (5 sites open)

Netherlands (2 sites open)

New Zealand (1 site open)

Norway (5 sites open)

Slovenia (1 site open)

Spain (8 sites open)

Switzerland (6 sites open)

UK (21 sites open)

Countries still in set-up since last update:

- Belgium
- Croatia
- Czech Republic
- France
- Ireland
- Italy
- Portugal
- Slovakia

New countries in set-up since last update:

- Austria
- Canada
- Germany
- Sweden

Several other participating National Coordinating Centres are progressing with country set-up, and many have made regulatory submissions.

The number of actively recruiting sites is continuously increasing. **So far, the FaR-RMS trial has 117 patients registered to study entry.**

The FaR-RMS trial has multiple research questions:

Phase 1b Dose Escalation Study – To find the dose of irinotrecan in combination with ifosfamide, vincristine and actinomycin-D. This question is open at ITCC and early phase approved centres.

So far, 9 patients have been recruited to this question.

Induction Chemotherapy (CT1a/b) – The CT1 randomisations will be open at all participating centres, upon completion of the Phase 1b question. These questions will compare the determined dose of irinotrecan in combination with ifosfamide, vincristine and actinomycin-D, against the current standard of care.

The CT1 questions will open upon completion of phase 1b.

Radiotherapy (RT1a/b/c, RT2) – The Radiotherapy randomisations are open to recruitment. These randomisations are delivered at all open sites where QUARTET approval has been obtained. The radiotherapy questions involve pre vs post-operative radiotherapy, dose-escalation in patients at higher risk of local failure and the role of radiotherapy to metastatic sites. An important aspect of the study focusses on the Quality of Life of patients when receiving radiotherapy.

So far, 4 patients have been recruited to the RT1a question.

So far, 6 patients have been recruited to the RT1b question.

So far, 16 patients have been recruited to the RT1c question.

So far, 4 patients have been recruited to the RT2 question.

Maintenance Chemotherapy (CT2a/b) – All sites will open to the maintenance randomisations. The purpose of the CT2 questions is to look at doubling the number of maintenance chemotherapy cycles compared to the current standard of care. Please note that some younger patients may not be able to swallow cyclophosphamide capsules. Where possible oral liquid cyclophosphamide should be prepared at sites. The UK has amended its clinical trial authorisation to allow powder for solution for injection to be mixed with sodium chloride for oral administration. Where countries need access to oral liquid formulations, country-specific options are being sought.

So far**, 6 patients** have been recruited to the CT2a question.

So far, **10 patients** have been recruited to the CT2b question.

Relapse (CT3) – The randomisation for patients with relapsed RMS will open in Feb 2022. The first new combination to be tested will be vincristine, irinotecan (VI) + regorafenib, a multityrosine kinase inhibitor, with VI + Temozolomide (VIT) as the control arm. The relapse study is an investigator-led collaboration between EpSSG and Bayer, the manufacturer of regorafenib.

The CT3 question is not currently open to recruitment but is due to open imminently.

Pathology

Risk group assignment and fusion status are integral part of the trial, molecular diagnostics on all cases of RMS should be carried out at the local centre. All samples will be centrally reviewed by the national pathology coordinator.

FDG-PET Sub-Study

If FDG PET-CT or FDG PET-MRI scanning is available at diagnosis & facilities allow, there will be the option for an additional scan after 3 courses of induction chemotherapy to determine retrospectively its prognostic value at centres that wish to participate. The prognostic value of response will be related to EFS and local failure free survival.

DW-MRI Sub-Study:

The aim of this sub-study is to investigate the prognostic value of DW-MRI imaging by comparing DW-MRI at diagnosis and at reassessment (After 3 cycles of chemotherapy for patients with localised disease).

Centres are encouraged to include diffusion-weighted series in their standard soft tissue sarcoma MRI protocols. Prinses Maxima and the EpSSG imaging group are leading this sub-study.

Quality of Life (QoL)

The TMG is working closely with the EpSSG PPI group to develop a more detailed assessment of QoL within the FaR-RMS study. The FaR-RMS study provides a unique platform to understand better the experience of patients of all ages, and their families. In addition to the QoL questions relating to the radiotherapy questions within the trial, further proposals are:

1. To extend quality of life study within FAR-RMS to correlate with a focus on the impact of local therapy (short- and longer-term outcomes) and to extend follow up duration to ensure long term QoL scores are measured. This will allow a more detailed understanding of the impact of local therapy for RMS.

2. Decision making study. This will explore the views of parents and older patients regarding their willingness to participate in clinical trials and attitude to their treatment. This will be limited to specific randomisation questions.

Other Sub-Studies in Development

Surgery

Impact of surgery (as part of local control) on short term and late toxicity and QoL.

Biology

Collection of samples, including liquid biopsies, to evaluate prognostic factors at diagnosis, response to treatment and disease recurrence.

Vinorelbine PK

To investigate the PK of IV and oral vinorelbine and explore opportunities for the use of oral vinorelbine in FaR-RMS.

New Logo

We are delighted to announce the new logo that will represent the FaR-RMS trial. This was designed by a young cancer survivor through a collaborative project with the Youth Forum at the Royal Marsden and several rhabdomyosarcoma survivors in conjunction with Alice's Arc, a children's cancer charity focused on rhabdomyosarcoma. We look forward to rolling the logo out across our communications about FaR-RMS.

Sponsor

The Study is coordinated through the Cancer Research Clinical Trials Unit in Birmingham, UK.

Parents and EpSSG 2021

DELPHINE HEENEN AND SARA WAKELING

FOCUS ON PATIENT/PARENTS GROUP

The parent group comprises individuals across 7 EpSSG countries (France, Italy, Netherlands, Norway, Denmark, Belgium and UK) and those with a mixture of paediatric sarcoma experiences and outcomes. The group strives to ensure that the patient/parent view is represented in the development and management of paediatric sarcoma clinical trials and research. In addition, the group seeks to establish communications between the EpSSG and parent/patient community regarding the clinical trials and their outputs. It also aims to further develop the role of patient advocates and the invaluable role they can play within the organisation. The group has been involved in a diverse range of activities to help achieve the EpSSG's organisational objectives and these are highlighted below.

1 - Involvement in clinical trials/Research

• FaR-RMS Trial • review and development of the lay summary for the newly devised relapse arm, which is due to launch imminently. • Attendance at the trial steering group meetings. • Input into the development and design of a new logo for the trial. This was conducted by a collaboration of young cancer survivors at the Royal Marsden and parent-led rhabdomyosarcoma children's charity, Alice's Arc. A young cancer survivor designed the logo, which will now appear on all communications and trial documentation. • participating in the design and development of research methods and questions for a project concerning Quality of Life on the trial. • MyKids Trial - attendance at the trial steering group meetings.

2 - Virtual Winter Meeting 2021

For the first time, this incorporated a session focused on parent, patient, involvement and engagement. Two parents were invited to present and answer questions on two initiatives. Delphine Heenen talked about the patient advocacy programme her organisation, KickCancer, has formed. This involves identifying and training a team of expert Belgium patient advocates who can devote time to KickCancer's advocacy activities by contributing to research projects or providing newly diagnosed patients with peer to peer support. Sara Wakeling and Joshua Stedford (Young cancer survivor/designer of the new logo) described the the story of the development of the new logo for the FaR-RMS trial.

They explained how multiple stakeholders were engaged, the generation of parent/patient led ideas, the formation of the design brief, logo design and the decision-making process.

3 - Developing a parent section on the EpSSg Website

The team commenced a project to design a parent-focused page on the website. This will provide parents with user-friendly information regarding paediatric sarcoma and clinical trial data.

4 - The future

The voice of parents and patients is becoming increasingly recognised in the formation of patient-centric research questions. We will explore and define how this role can have more impact within the EpSSG setting. Additionally, we hope to involve some paediatric sarcoma cancer

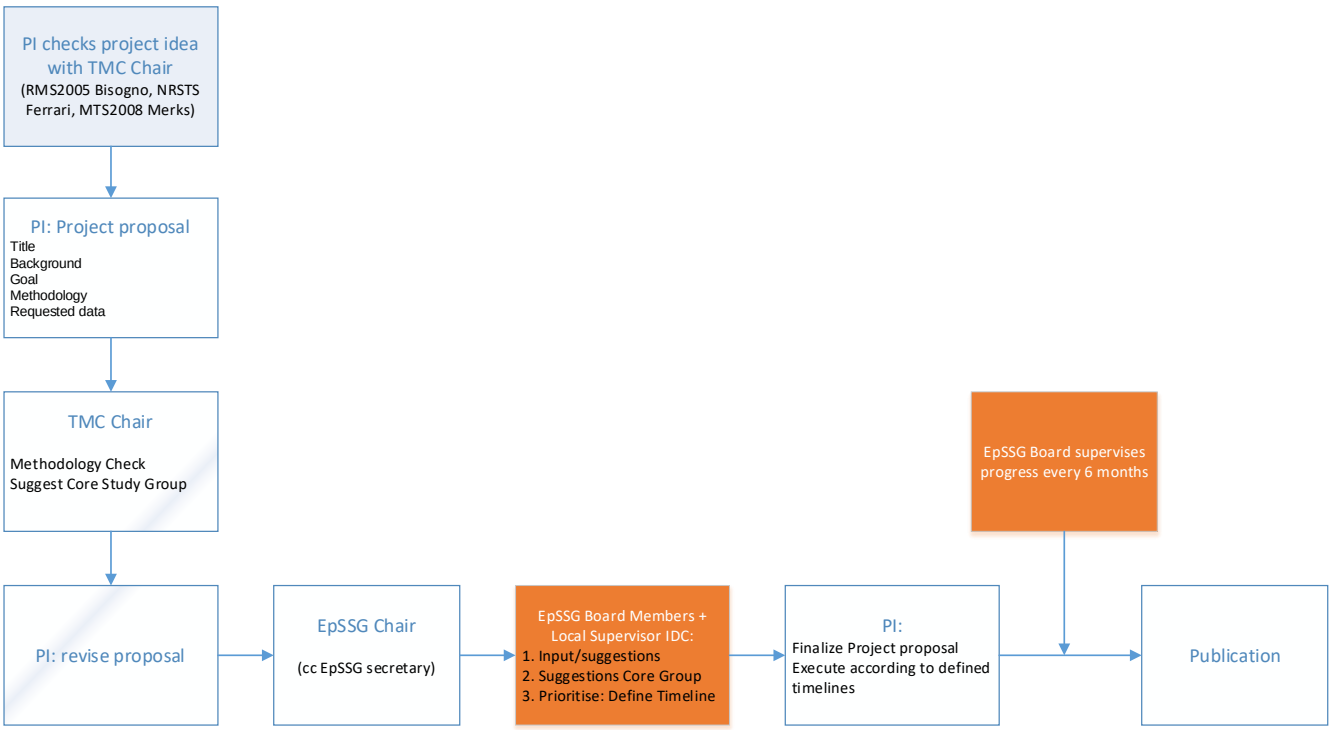
survivors within the group in the future. There are challenges associated to the level of impact the patient/parent group can have and these involve identifying patients/parents who have sufficient time to carry out the tasks and ensuring the best levels of collaboration between the patients/parents and the EpSSG medical community.

We are proud to be a part of the EpSSG and look forward to the year ahead!.'

New study proposals are welcome

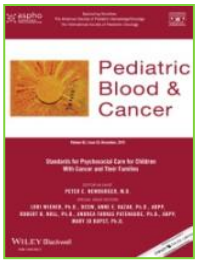
(By Prof. Gianni Bisogno, Hans JHM. Merks & IDC)

The International Data Center (IDC) together with different PI's are working on many analyses in parallel to translate all the knowledge we gathered through our clinical trials into publications in peer reviewed journal to share this with professionals across the globe. In particular, a scheme is reported below. This explains the steps every PI should take before starting a project/analyses.



EpSSG Study proposal Flow diagram

Papers in 2021



- **1. Alveolar rhabdomyosarcoma with regional nodal involvement: Results of a combined analysis from two cooperative groups.** Pediatr Blood Cancer. 2020 Nov 27; e28832. PMID: 33245207, PMCID: PMC8414760, DOI: 10.1002/pbc.28832

Author Soledad Gallego & EpSSG members

Treatment of children and adolescents with alveolar rhabdomyosarcoma (ARMS) and regional nodal involvement (N1) have been approached differently by North American and European cooperative groups. In order to define a better therapeutic strategy, we analyzed two studies conducted between 2005 and 2016 by the European paediatric Soft tissue sarcoma Study Group (EpSSG) and Children's Oncology Group (COG). We retrospectively identified patients with ARMS N1 enrolled in either EpSSG RMS2005 or in COG ARST0531. Chemotherapy in RMS2005 comprised ifosfamide + vincristine + dactinomycin + doxorubicin (IVADo), IVA and maintenance (vinorelbine, cyclophosphamide); in ARST0531, it consisted of either vincristine + dactinomycin + cyclophosphamide (VAC) or VAC alternating with vincristine + irinotecan (VI). Local treatment was similar in both protocols.

The analysis of the clinical characteristics of 239 patients showed some differences between study groups: in RMS2005, advanced Intergroup Rhabdomyosarcoma Study Group (IRS) and large tumors predominated. There were no differences in outcomes between the two groups: 5-year event-free survival (EFS), 49% (95% confidence interval [CI]: 39-59) and 44% (95% CI: 30-58), and overall survival (OS), 51% (95% CI: 41-61) and 53.6% (95% CI: 40-68) in RMS2005 and ARST0531, respectively. In RMS2005, EFS of patients with FOXO1-positive tumors was significantly inferior to those with FOXO1-negative (49.3% vs 73%, P = .034). In contrast, in ARST0531, EFS of patients with FOXO1-positive tumors was 45% compared with 43.8% for those with FOXO1-negative.

Conclusions: The outcome of patients with ARMS N1 was similar in both protocols. However, patients with FOXO1 fusion-negative tumors enrolled in RMS2005 showed a significantly better outcome, suggesting that different strategies of chemotherapy may have an impact in the outcome of this subgroup of patients.

2. Embryonal rhabdomyosarcoma completely resected at diagnosis: The European paediatric Soft tissue sarcoma Study Group RMS2005 experience European Journal of Cancer, Vol 146, March 2021, 21-29. PMID: 33567392 DOI: 10.1016/j.ejca.2020.12.025

Author Christophe Bergeron & EpSSG members

We report the results of the European paediatric Soft tissue sarcoma Study Group (EpSSG) RMS 2005 study, which prospectively evaluated the reduction of chemotherapy in patients with embryonal RMS (ERMS) after initial surgery.

Between October 2005 and December 2016, all patients with localised ERMS with an initial microscopically complete resection (IRS group I) with lymph node-negative (N0) were prospectively enrolled in the low-risk (n = 70, subgroup A; age < 10 years and tumour size ≤ 5 cm) or standard-risk group (n = 108, subgroup B;

age ≥ 10 years or tumour size > 5 cm. Subgroup A received 8 courses of vincristine and dactinomycin (VA) for 22 weeks; subgroup B received 4 courses of VA with ifosfamide (IVA) and 5 courses of VA for 25 weeks.

Results: The 5-year event-free survival (EFS) and overall survival (OS) were 90.8% (95% confidence interval [CI]: 85.0-94.4) and 95.7% (95% CI: 90.5-98.1), respectively (n = 178). The EFS and OS were 95.5% (95% CI: 86.8-98.5) and 100% (subgroupA), and 87.8% (95% CI: 79.3-93.0) and 93.0% (95% CI: 84.8-96.8)(subgroup B), respectively. Bearman stage 2 veno-occlusive disease (VOD) occurred in 4 very young patients.

Conclusion: VA treatment for 8 courses was effective and well tolerated by the subgroup of patients with low-risk ERMS (group A). Four courses of IVA and 5 courses of VA instead of 9 courses of IVA also has very good results. Careful monitoring for liver toxicity is important in very young patients. European union drug regulating authorities clinical trials EUDRACT No. 2005-000217-35.

3. Pathology of childhood rhabdomyosarcoma: A consensus opinion document from the Children's Oncology Group, European Paediatric Soft Tissue Sarcoma Study Group, and the Cooperative Weichteilsarkom Studiengruppe. Pediatr Blood Cancer. 2021 Mar;68(3):e28798. doi: 10.1002/pbc.28798. PMID: 33306276 DOI: 10.1002/pbc.28798

Author: EpSSG, CWS and COG colleagues

The diagnosis and classification of rhabdomyosarcoma (RMS) has undergone several shifts over the last 30 years. While the main diagnostic categories remained the same, changes in the histologic criteria necessary for diagnosis, as well as varied reliance on immunohistochemical and molecular data over time, have created confusion, particularly regarding how these shifts impacted risk stratification and enrollment onto clinical trials. The goal of this report is to review the evolution and current status of RMS diagnosis, focusing on diagnostic criteria in the Children's Oncology Group (COG), the European Paediatric Soft Tissue Sarcoma Group (EpSSG), and the Cooperative Weichteilsarkom Studiengruppe (CWS). In addition, we emphasize research tools used to classify RMS and address biological questions within current clinical trials run by each group. The INternational Soft Tissue SaRcoma ConsorTium (INSTRuCT) initiative will maximize potential to optimize risk stratification by recognizing and accounting for differences in historical data and current practices.

4. Non-parameningeal head and neck rhabdomyosarcoma in children, adolescents, and young adults: Experience of the European paediatric Soft tissue sarcoma Study Group (EpSSG) - RMS2005 study Eur J Cancer 2021 Jul;151:84-93. doi: 10.1016/j.ejca.2021.04.007. Epub 2021 May 7. PMID: 33971448 DOI: 10.1016/j.ejca.2021.04.007

Author: Heidi Glosli & EpSSG colleagues

The primary aim of this study was to analyse and evaluate the impact of different local treatments on the pattern of relapse in children with primary head and neck non-parameningeal (HNnPM) rhabdomyosarcoma (RMS), treated in the European paediatric Soft tissue sarcoma Study Group (EpSSG) RMS2005 study. The secondary aim was to assess whether current risk stratification is valid for this specific site.

This study includes all patients with localised HNnPM RMS enrolled in the RMS2005 study between 2005 and 2016. Treatment comprised chemotherapy adapted to risk group, with local surgery and/or radiation therapy. The main outcome measures were event-free survival (EFS) and overall survival (OS).

A total of 165 patients were identified; the median age was 6.4 years (range, 0.1-25). The most common tumour sites were cheek/chin (22%) and nasal ala/nasolabial fold (20%). Histology was unfavourable for 40%, and regional nodal involvement present in 26%. Local therapy included surgery (58%) and/or radiotherapy (72%) to primary tumour and/or regional lymph nodes. After a median follow-up of 66 months (range, 6-158), 42 patients experienced an event, and 17 are still alive. Tumour events were frequent in oral primary (36%), parotid site (26%), cheek/chin (24%), and nasal ala/nasolabial fold (24%) and included locoregional failure in 84% of cases. The 5-year EFS and OS were 75% (95% confidence interval [CI]: 67.3-81.2) and 84.9% (95% CI: 77.5-89.7), respectively. Favourable histology was associated with a better EFS (82.3% versus 64.6%; p = 0.02) and nodal spread with a worse OS (88.6% versus 76.1%; p = 0.04). Different sublocations within the HNnPM primary did not have significant impact on outcome.

Conclusion: Locoregional relapse/progression is the main tumour failure event in this site. Despite frequent unfavourable risk factors, HNnPM RMS remains a favourable location in the context of a risk-adapted strategy.

5. Paediatric non-rhabdomyosarcoma soft tissue sarcomas: the prospective NRSTS 2005 study by the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) The Lancet Child & Adolescent Health June 2021, doi: 10.1016/S2352-4642(21)00159-0

Authors: Andrea Ferrari & EpSSG colleagues (see NRSTS Committee Report)

6.The Impact of Radiation Therapy in Children and Adolescents With Metastatic Rhabdomyosarcoma. Int J Radiat Oncol Biol Phys. 2021 Jul 1:S0360-3016(21)00823-3. doi: 10.1016/j.ijrobp.2021.06.031. PMID: 34217789 DOI: 10.1016/j.ijrobp.2021.06.031

Author: Alison Cameron & EpSSG colleagues

Purpose: There is limited evidence to define the role of radiation therapy in children with metastatic rhabdomyosarcoma (mRMS). In the international BERNIE study, children with mRMS or non-RMS soft tissue sarcoma were randomized to receive standard chemotherapy with or without bevacizumab, with radiation therapy to all disease sites recommended after chemotherapy cycle 6. We retrospectively evaluated the impact of radiation therapy on survival in the mRMS cohort.

Patients were grouped according to the radiation therapy they received: radical, partial, or none. Radical irradiation was defined as radiation therapy delivered to all disease sites, unless a site was completely surgically resected. Partial irradiation was defined as radiation therapy to ≥1, but not all, disease sites. Landmark analysis excluded patients with an event before day 221. Overall survival (OS) and event-free survival (EFS) were modeled using Cox proportional hazards models.

Of 102 patients with mRMS, 97 were included in the analysis for OS and 85 for EFS. Overall, 27 patients received radical irradiation, 46 partial irradiation, and 24 no irradiation. EFS was not significantly different among patient groups after adjustment for prognostic factors (hazard ratio [HR] = 0.520; P = .054 for any vs no irradiation). Radiation therapy was associated with improved OS compared with no radiation therapy (adjusted HR = 0.249; P = .00025), with OS being greater for radical versus partial irradiation (HR = 0.245; P = .039). The 3-year OS rate was 84%, 54%, and 23% for patients receiving radical, partial, and no irradiation, respectively. Radical treatment (surgery, irradiation, or both) of the primary site improved EFS and OS compared with no treatment.

Conclusions: These findings demonstrate variability in the application of radiation therapy for mRMS and support the routine use of radical treatment to the primary site. Radical irradiation to metastatic sites may

further improve OS. The burden of such treatment should be balanced against prognosis; further studies are needed.

7. Randomized Phase II Trial of Vincristine-Irinotecan With or Without Temozolomide, in Children and Adults With Relapsed or Refractory Rhabdomyosarcoma: A European Paediatric Soft tissue Sarcoma Study Group and Innovative Therapies for Children With Cancer Trial. J Clin Oncol. 2021 Aug 3:JCO2100124. doi: 10.1200/JCO.21.00124. Online ahead of print.PMID: 34343032PMID: 34343032 DOI: 10.1200/JCO.21.00124

Author: Anne Sophie Defachelles & EpSSG colleagues (see NRSTS Committee Report)

8. Role of 18F-FDG-PET/CT in the staging of metastatic rhabdomyosarcoma: A report from the European paediatric Soft tissue sarcoma Study Group

PMID: 34385068 DOI: 10.1016/j.ejca.2021.07.006

Author: Federico Mercolini & EpSSG colleagues

The aim of this study was to evaluate the ability of ^{18}F-FDG-PET/CT in the staging of metastatic rhabdomyosarcoma patients, compared to the standard radiology workup (SRW) and to bone marrow aspirates/bone marrow biopsies. Thanks to the great collaboration of the EpSSG centers, the reports of 118 of 121 eligible patients for this study, enrolled in the EpSSG RMS 2008 protocol, were obtained.

The imaging (^{18}F-FDG-PET/CT and MRI/CT-scan/bone scan) reports were systematically reviewed by two authors supported by a nuclear medicine doctor; the number and sites of metastatic lesions detected by SRW and ^{18}F-FDG-PET/CT were noted. The sensitivity of the different investigation methods was calculated using as reference the final clinical interpretation by the treating physician, i.e. if the lesion demonstrated by the radiological investigations were considered, and treated, as a metastasis or not.

In 4 patients (3.4%), ^{18}F-FDG-PET/CT changed the staging from localized to metastatic disease and revealed a greater number of sites of metastasis (mean 1.94/patients, compared to 1.72/patients of SRW).

^{18}F-FDG-PET/CT showed a higher sensitivity than SRW in recognizing locoregional (96.2% vs. 78.5%, p-value = 0.0013) and distant (94.8% vs. 79.3%, p-value = 0.0242) nodal involvement. Conversely, the sensitivity was lower for intrathoracic sites (lung 79.6% vs. 100%, p-value=0.0025).

For bone metastasis, ^{18}F-FDG-PET/CT was more sensitive than bone scintigraphy (96.4% vs. 67.9%, p-value=0.0116). The ^{18}F-FDG-PET/CT sensitivity and specificity to detect marrow involvement were 91.8% and 93.8%, respectively.

These findings lead to important conclusions: first, the greater sensitivity of ^{18}F-FDG-PET/CT compared to other radiological techniques, in particular for lymph node involvement (frequent site of involvement in rhabdomyosarcoma), reinforces the recommendations for its use in initial diagnostics; second, for the study of bone involvement, if ^{18}F-FDG-PET/CT is available can replace the bone scan; third, chest-CT remains essential to detect lesions in intrathoracic sites, which can be performed in a one stop-shot routine examination or on a dedicated chest-CT scan.

^{18}F-FDG-PET/CT therefore plays an important role in rhabdomyosarcoma and will be the subject of further studies in the new EpSSG FaR-RMS protocol.

9. Congenital rhabdomyosarcoma: A report from the European paediatric Soft tissue sarcoma Study Group

PMID: 34582098 DOI: 10.1002/pbc.29376

Author Gianni Bisogno & EpSSG colleagues

Rhabdomyosarcoma (RMS) is one of the most common soft tissue sarcomas of childhood, but it is a rare condition in neonates (1–2% of cases). Different studies have reported even a poorer prognosis at this age challenging the treatment decision with chemo or radio therapy.

The European paediatric Soft tissue sarcoma Study Group analyzed this rare condition of 24 patients in the first 2 months of life diagnosed with localized or metastatic congenital RMS from October 2005 to December 2016.

Patients, tumor features, as well as treatment modality and outcome were reported. All, except one patient had a favorable localized disease. Complete tumor resection was possible for 10 patients. The dose reduction was considered for all according to age and weight. No radiotherapy was given to them. After 5-years of follow-up, 75% of these patients never relapsed. Moreover, they had a good survival rate of 87.3%.

Our study concluded that patients with congenital RMS with favorable disease, adjusted dose of chemotherapy and without irradiation treatment present a good overall survival.

NRSTS Projects (BY DR. ANDREA FERRARI & DR. DANIEL ORBACH)

THE EPSSG NRSTS COMMITTEE IS STILL WORKING ON THE DEVELOPMENT OF A NEW STUDIES DEDICATED TO NRSTS ACROSS EUROPE.

The EpSSG NRSTS Committee is soon to start new protocol dedicated to NRSTS, called **MYKIDS - Molecular Identification and Characterization of non-Rhabdomyosarcoma Soft Tissue Sarcoma in Kids, Adolescents and Young Adults: an EpSSG NRSTS study.**
The MYKIDS study is designed to better understand the molecular diagnosis of pediatric NRSTS in view of optimal treatment. In particular, to a) understand the role of molecular profiling in pediatric NRSTS, b) enable a comprehensive decision on the treatment for individual patients, c) compare molecular profiles to histological grading for prognostification, and d) use molecular diagnostics to study non-invasive diagnosis (liquid biopsies).
Co-principal investigators of the study are Max van Noesel (Princess Máxima Center, Utrecht), Daniel Orbach (Institut Curie, Paris) and Andrea Ferrari (Istituto Nazionale Tumori, Milan).

In parallel, the NRSTS Committe is working on two other prospective therapeutic projects:
joining forces with the CWS group to develop a randomised phase II trial dedicted to pediatric desmoid-type fibromatosis, aiming to evaluate efficacy and safety of the oral combination vinorelbine- methotrexate
(**Desmover** study, PI – Nadege Corradini, Leon Berard, Lyon).
REACH NRSTS project - REgorafenib in young adults, **A**dolescents and **C**hildren with **H**igh-risk **NRSTS** – exploring whether the addition of **Regorafenib** to standard Ifosfamide-Doxorubicine chemotherapy improve outcome in

high-risk NRSTS (PIs – Susanne Gatz, Andrea Ferrari).

In the last years, the NRSTS Committee has reported several analyses of specific histological subgroups. In 2021, the whole series of patients enrolled in the EpSSG NRSTS 2005 study has been published.

Ferrari A, et al. Paediatric non-rhabdomyosarcoma soft tissue sarcomas: the prospective NRSTS 2005 study by the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG). Lancet Child Adolesc Health. 2021 Aug;5 (8):546-558.

The series reports the results of the two prospective, non-randomised, historically controlled trials (one on localised adult-type NRSTS and the other on localised synovial sarcoma) done at 100 academic centres and hospitals in 14 countries. The analysis included 569 patients (out of a total of 1321 cases registered in the NRSTS 2005 study from May 2005 to December 2016. With a median follow-up of 80 months, 5-year EFS and OS were 73.7% and 83.8%, respectively. Together with the COG ARST0332 trial, this study represents a turning point and a benchmark for the management of paediatric NRSTS, defining the risk-adapted standard of care. As major fidings, the study showed that adjuvant treatment can be safely omitted in the low-risk population (classified here as the surgery alone group). Improving the outcome for patients with high-risk, initially resected adult-type NRSTS and those with initially unresectable disease remains a major clinical challenge. In particular for unresected cases, this study showed favourable results by comparison with previous series: neoadjuvant ifosfamide plus doxorubicin chemotherapy seemed to improve the resectability rate compared with previous studies.

For 2022, the analysis of other subgroups are planned, i.e. ectomesenchymoma, epithelioid hemangioendothelioma, axial infantile fibrosarcoma, desmoplastic small round cell tumors, metastatic NRSTS.

The NRSTS committee continues to collaborate within the **INSTRUCT project** (INternational Soft Tissue SaRcoma ConsorTium) to promote transatlantic cooperation and data sharing on pediatric soft part sarcomas. Clinical data from previous European (SIOP MMT, EpSSG, ICG, CWS) and American (COG) NRSTS studies will soon be ready to be analyzed to improve knowledge on such rare sarcomas. Projects are on going on "Challenging and controversies in pediatric soft part sarcomas" and "Consensual definitions on NRSTS margins".

Early phase trials committee

(by Susanne Gatz)

Ongoing Early Phase Trials in Europe enrolling STS patients

The committee continues to provide an update on Early Phase trials in Europe, the latest update is being published with this report.

Closed and opening trials with particular relevance

VIT 0910

The VIT-0910 trial was the first study of the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) to focused on relapsed or

refractory RMS. This trial randomly assigned patients age 6 months to 50 years with relapsed/refractory RMS to 21-day cycles of VI with and without temozolomide. The control arm (which only received VI) was selected based on results of the ARST0121 trial, which found a shorter regimen of VI had the same good efficacy as VI administered in a protracted schedule among adults and children with relapsed/refractory RMS. The goal of the trial was to help better define the standard chemotherapy regimen for relapsed cases, to which novel agents could be added or other innovative therapies compared. The primary endpoint was overall response rate after two cycles of chemotherapy. Secondary endpoints were progression-free survival, OS, and adverse events (AEs).

Results indicated a benefit of the combination chemotherapy, with an overall response rate of 44% in the VI plus temozolomide (VIT) arm (24 of 55 evaluable patients) and 31% in the VI arm (18 of 58 patients) for patients with relapsed RMS. OS was significantly better with VIT (adjusted HR 0.55), with consistent results for reduction in risk of disease progression or relapse. Despite these benefits, toxicity was a concern in patients treated with VIT, with 98% experiencing grade 3 or higher AEs, compared with 78% of patients receiving VI only. Serious treatment-related AEs were also more common in VIT treatment than control (38% vs. 19%). Based on results from this trial, VIT combination therapy is now considered in Europe to be the new preferred treatment for patients with relapsed RMS who have previously received an alkylating agent.

Building on the success of this trial, the EpSSG have implemented a multi-arm, multistage study exploring frontline treatment of relapsed RMS (NCT04625907<https://clinicaltrials.gov/ct2/show/NCT04625907>) in which VIT will be the control arm for relapsed disease. The increased toxicity with VIT in the VIT-0910 trial raises the question of whether it will be possible to add new targeted therapy or immunotherapy to this chemotherapy. The first new combination to be tested will be VI with the tyrosine kinase inhibitor regorafenib.

Anne Sophie Defachelles and EpSSG colleagues 2021

REGORAFENIB within FaR-RMS

The multi TKI Regorafenib is the first novel agent which will be evaluated in the FaR-RMS study in the relapse setting. The established gold standard in RMS relapse of Vincristine/ irinotecan/ temozolomide is being compared to the combination of Vincrsitine/ irinotecan and regorafenib. The study has been developed with significant input from members of the Early Phase trials committee. This FaR-RMS study part is funded by BAYER and delivered by the sponsor (CRCTU/ University of Birmingham) to filing standards and allows BAYER to comply with their paediatric investigation plan (PIP). BAYER is also funding the comprehensive biomarker package which includes comprehensive molecular profiling, ctDNA analysis and functional imaging analysis (DCE-MRI) in the relapse setting in both treatment arms. Recruitment start is imminent.

VOLASERTIB within FaR-RMS

The committee remains keen to incorporate volasertib in the FaR-RMS platform trial as a Phase Ib study in combination with vincristine in the relapsed/refractory setting. Negotiations with Oncoheroes are ongoing.

Collaboration with Biology committee

The committee continued their collaborative work with the EpSSG Biology Committee to identify promising new targets and agents for the FaR-RMS trial and other indications. Two further EpSSG biology/ early Phase committee workshops were held this year; whilst the first workshop was again focusing on specific targets/ drugs going forward the joint groups decided to focus on more generic themes to improve our understanding how certain aspects of tumour biology affect therapy and how they can be

modelled and targeted – these broader themes include: Maintenance therapy, immunotherapy and epigenetics in STS.
The two workshops held were:
19th April 2021: Sonic Hedgehog pathway, WEE1 inhibitors and PI3K/MEK pathways were discussed from the biological and drug development/ clinical angle with focus on RMS.
22nd November 2021: topic "Maintenance Therapy in RMS – what it is and how to improve it – from bedside to bench and back again"
A review publications of the workshop initiative is planned. The maintenance workshop led to forming two groups between the committees – a liquid biopsy group and a preclinical model group.

Research into specific patient groups with unmet clinical need

The early Phase committee (PI V Minard) has initiated a project on RMS patients with localised disease and disease progression based on discussions during the EpSSG winter meeting 2021. The study will aim to look at pathology/ clinical data and molecular correlates in patients on the RMS2005 study. The project will include members of other relevant sub-committees.

SIOPE-ITCC-EpSSG sessions during SIOPE meeting

The Early Phase trial committee significantly contributed to the SIOPE-ITCC-EpSSG sessions held virtually at SIOPE 2021. The session in 2021 focused on RMS from molecular profiling data, early Phase trial opportunities in Europe, the EpSSG biology/early phase committee workshops and the close collaboration with the new ITCC structure.

Collaboration with the NRSTS committee

NRSTS will be a key topic for the early Phase committee going forward. One key collaboration in this regards is the new collaboration with the NRSTS committee and the development of REACH-NRSTS – a randomized, controlled trial of REgorafenib in young adults, Adolescents and Children with High risk NRSTS in the frontline setting (PIs – Susanne Gatz, Andrea Ferrari). Members of both committees are working together on this since April 2021 and CRCTU/University of Birmingham will be the international sponsor. The study will be closely linked with the MYKIDS study and translational research and retrospective linking of responses with molecular profiling data will be key to make progress in this diverse group of tumours.

FINANCIAL STATEMENT 2021 (BY DR. A. FERRARI, JHM. MERKS)

An accountancy and treasurer's Report of the final year's account was presented and approved during the EpSSG Spring meeting Assembly held virtually in March 23, 2022 during the 3rd SIOPE Annual Meeting.

Total income for the association in 2021 was €24.055,83, mainly from members' fees, meeting registration and donations from Pharma. Interest on accounts and investments was €1494,28.
Total expenses were almost €27.892.

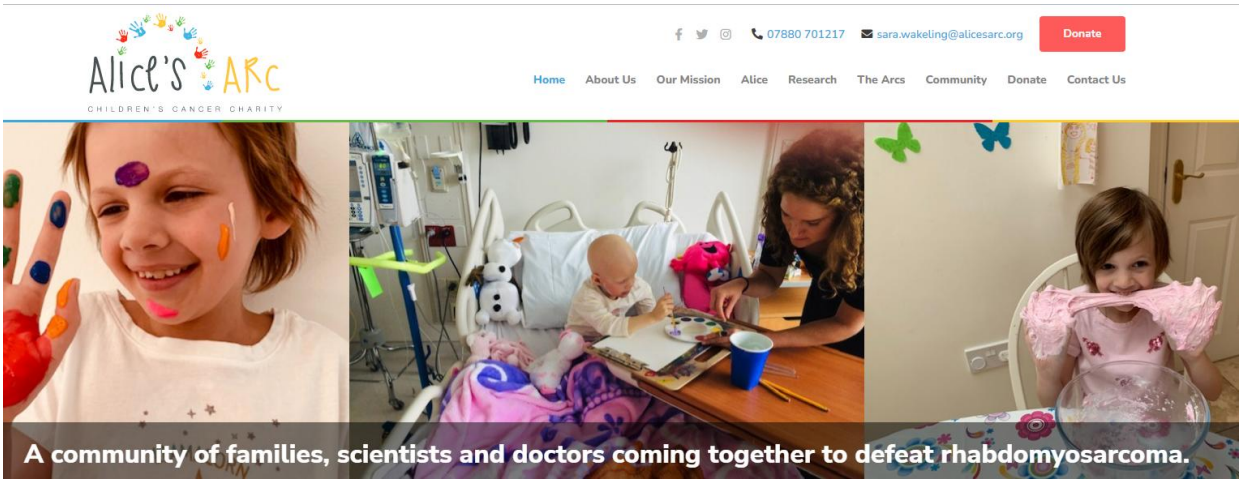
For 2022 we expect income from EpSSG membership fees and meeting fees from our Winter meeting; we aim to negotiate with Pharma whenever we substantially invest our expertise and network into Paediatric Investigation.

Plans or other work. As our association is vital to maintain both expertise and the clinical network this justifies financial support from parties that need substantial input from EpSSG members.
Funding Sources for 2022: EpSSG will receive financial support from Alice's Arc Foundation to support our EpSSG scientific project manager and statistician for the year 2022. We are grateful to

Sara Wakeling and the trustees of Alice's Arc for the support so crucial for our scientific network organization.
Grateful to those who help implementing work resources in research.

WORKPLAN in 2022

Continue to open the FaR-RMS study in countries and centers not open yet.
Implement and optimize participation in sub-studies to FaR-RMS including Imaging and Biology Biomarker studies
Open the MYKIDS Study and initiate the study across EpSSG countries.
Finalize the DESMOVER study to strive for opening of the study in 2023
Efficient preparation of reports by the International Data Center (IDC) in close collaboration with PI of each project leading to timely delivery of manuscript.
Consolidate funding for EpSSG IDC and secretariat activities essential for our network organization of professionals to optimally function and create scientific reports.
Optimize collaboration with parents through involvement at meetings and in projects.
Optimize communication with members through our EpSSG website and mailings on important EpSSG developments
Aim for a live Winter meeting in Rome to nurture our important professional network



WE HAVE A DONATION BUTTON ON OUR WEBSITE! HELP US SPREAD THE WORD!

The EpSSG coordinates European international clinical trials aimed at improving the treatment of soft tissue sarcoma (STS). Through research our goal is to improve the quality of care offered to children, teenagers and young adults with

STS and to improve the outcomes of treatment.Your donation will help to support the team of clinicians, scientists, statisticians and data managers in developing and running new clinical trials in paediatric STS in order to help future generations of children with STS.

Association past meetings - Calendar 2020-2021

DATE	MEETING	LOCATION	NOTES
2020			
May 4-8 (Mo-Fri)	EpSSG Spring Meeting & Association Assembly	SIOPE Congress, Valencia Spain	NOT HELD! Pandemic emergency
December 3-4 (Th-Fr)	EpSSG Winter Meeting & Association Assembly	Virtual Meeting	Virtual Meeting
2021			
April 26-30 (Mo-Fri)	EpSSG Spring Meeting & Association Assembly	SIOP Europe 2021 2nd Annual Meeting Virtual	Virtual Meeting
December 2-3(We-Fri)	EpSSG Winter Meeting & Association Assembly	Virtual Meeting	Virtual Meeting

Association future meetings -Calendar 2022-2023

DATE	MEETING	LOCATION	NOTES
2022			
March 23 (Wed)	EpSSG Spring Meeting & Association Assembly	SIOP Europe 2021 2nd Annual Meeting Virtual	Performed
November 30-December 2 (Wed-Fr)	EpSSG Winter Meeting & Association Assembly	Rome	Confirmed
2023			
May 8-12(Mo-Fri)	EpSSG Spring Meeting & Association Assembly	SIOP Europe 2021 2nd Annual Meeting Valencia	Confirmed
November 30-December 1 (Th-Fri)	EpSSG Winter Meeting & Association Assembly	Barcelona	To be confirmed