ANNUAL REPORT 2024

The European Paediatric Soft tissue sarcoma Study Group

Summary

THE E*p*SSG ASSOCIATION

The European *paediatric* Soft tissues sarcoma Study Group (E*p*SSG) is an international organization of professionals dedicated to the care and treatment of children and young people with soft tissue sarcomas (STS). This includes the most common STS, rhabdomyosarcoma (RMS), as well as a diverse group of other tumors collectively referred to as Non-Rhabdomyosarcoma or Adult-type Soft Tissue Sarcomas (NRSTS).

The official legal body representing EpSSG's activities is the EpSSG Association. Its mission is to promote and manage clinical trials, support both clinical and basic research, foster the highest standards of care, organize educational events for members and healthcare professionals, and advocate for children and young people affected by STS.

EpSSG is legally and administratively based in Padua, Italy since 2009.

In 2024, it became recognized as an ETS (Third Sector Entity) Association—granting it greater visibility within Italy and enabling access to funding opportunities such as the "5 per mille" donation scheme and public sponsorships.

EpSSG actively collaborates with counterpart organizations across Europe, North America, and beyond. In particular, it has maintained a close partnership with the Cooperative Weichteilsarkom Studiengruppe (CWS) in Europe. As of December 2024, CWS countries have formally integrated into the EpSSG, with the two groups merging to form a single unified association. Consequently, the EpSSG now serves as the representative body for the entirety of Europe.

Since 2016, EpSSG has welcomed the involvement of parents of sarcoma patients, who have made valuable contributions in supporting and shaping the group's initiatives.

This report provides a summary of EpSSG's key activities in 2024.

For more information, please visit the EpSSG website: www.epssgassociation.it.

One united European paedatric Soft Tissue Sarcoma Study Group:

Countries of Cooperative Weichteilsarkom Studiengruppe (CWS) are now part of EpSSG

(By Prof. Monika Sparber-Sauer and Prof. Martin Ebinger)

Since the 1970s, several European study groups had existed, including the AIEOP Soft Tissue Sarcoma Committee (formerly ICG), the SIOP Malignant Mesenchymal Tumours (MMT) Committee, and the Cooperative Weichteilsarkom Studiengruppe (CWS), covering Germany, Austria, Sweden, Finland, Poland, and Switzerland. In 1996, after agreeing on risk group definitions for RMS tumours, parallel trials began: VAIA vs. CEVAIE in the CWS/ICG group, and IVA vs. CEVAIE in the MMT group. In 2005, these groups founded the EpSSG, launching the RMS 2005 protocol. However, CWS could not join due to funding and

legal barriers, leading to disappointment and mistrust. CWS continued independently, treating patients according to its guidance and registering them in SoTiSaR, while also conducting the CWS-2007 HR study.

In 2016, Monika Sparber-Sauer met EpSSG colleagues and soon joined meetings. Collaboration intensified through joint analyses, and in 2021 she and Martin Ebinger became CWS chairs, applying for funding to join the FaR-RMS study. Germany secured funding in 2024, with CWS focusing on translational research, liquid biopsies, and innovative trials such as PerVision. In October 2024, the EpSSG board invited CWS to join, and on 6 December 2024 Monika and Martin were elected to the EpSSG board. From then on, a united EpSSG has represented Europe, dedicated to improving treatment and outcomes for patients with soft tissue sarcomas. On behalf of the former CWS, we are honoured and grateful for the trust placed in us.

EpSSG BOARD

Prof. Hans Merks	• Chairman - Utrecht, The Netherlands
Dr. Timothy Rogers	• Treasurer, Bristol, UK
Prof. Veronique Minard-Colin	• Paris, France
Dr. Michela Casanova	• Milan, Italy
Dr. Henry Mandeville	• Sutton, UK
Prof. Andrea Ferrari	• Milan. Italy
Dr. Gabriela Guillén Burrieza	• Barcelona, Spain
Dr. Nadège Corradini	• Lyon, France
Dr. Lisa Hjalgrim	• Copenhagen, Denmark
Dr. Julia Chisholm	• Sutton, UK
Dr. Daniel Orbach	• Paris, France
Prof. Gianni Bisogno	• Padova, Italy
Prof. Monika Sparber-Sauer	• Stutgart, Germany
Prof. Martin Ebinger	• Tuebingen Germany

Board meetings were held remotely in 2024 each second Monday of the month: January 8th , February 12th, March 11th , April 8th, May 13June 10th , July 8th, September 9nd, October 14th and November 11th . The board met in person in Milano in May and Paris in December 2024, the day before the SIOPE and Winter meetings. In Paris, we took the opportunity to thank Véronique, Michela, and Henry at the end of their term, expressing our deep gratitude for their outstanding contributions and collaboration. We also warmly welcomed the new Board members: Julia Chisholm, Gianni Bisogno, Daniel Orbach and two members from Germany, welcoming CWS countries joining EpSSG: Monika Sparber-Sauer and Martin Ebinger.

New board members entering the board Dec 2024: short bio

Julia Chisholm, Consultant Paediatric and Adolescent Oncologist specialising in soft tissue sarcoma and drug development at the Royal Marsden, Hospital, Sutton, UK and Reader at the Institute of Cancer Research, Sutton. She has been an EpSSG member for around 20 years and had held several EpSSG positions previously, including Chair of the Phase I/II Committee (2010-16) and Board Member (2013-2019).

Daniel Orbach MD, Paediatric Oncology Department, Institut Curie (since 1998), associate director (clinic) of the SIREDO center (Care, Innovation and Research for children and AYA with cancer), since 2017 in Paris. He has been an EpSSG member since its foundation.

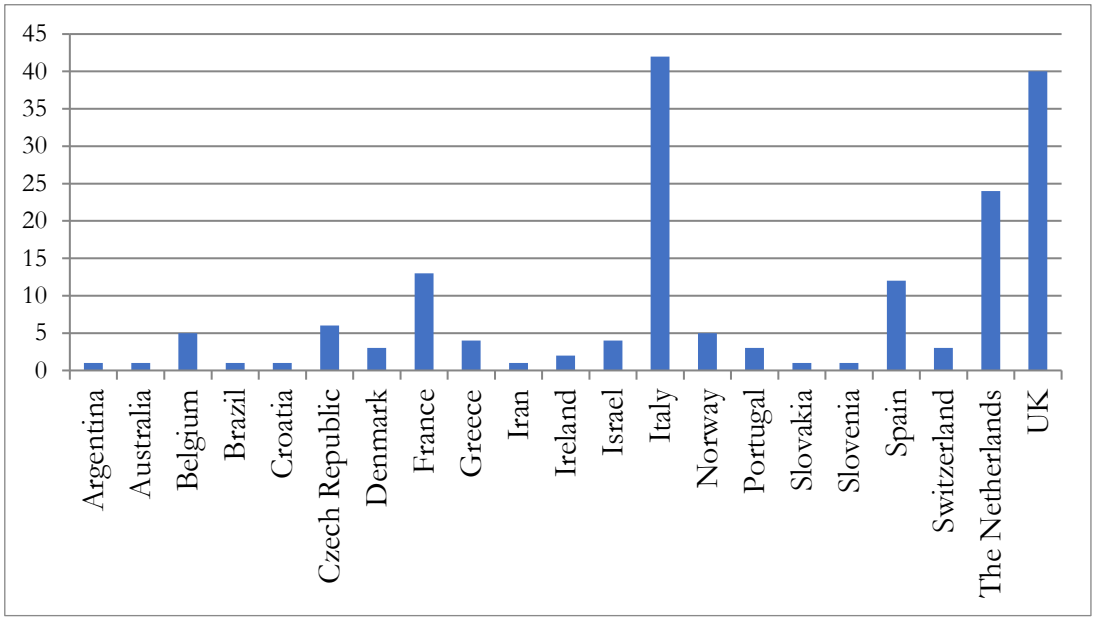
Gianni Bisogno Professor of Pediatrics and Consultant Pediatric Oncologist at the Department of Woman's and Child's Health, University of Padova, Italy. He is one of the founders and chair (2013-2019) of the EpSSG. Since 2024, he is the chair of the RMS Working group of EpSSG.

Monika Sparber-Sauer Senior Pediatric Oncologist at Olgahospital Klinikum Stuttgart and University Children`s Hospital of Tübingen. Her dedicated research field are Non-rhabdomyosarcoma and rare sarcoma since more than 10 years and nowadays Rhabdomyosarcoma. Since 2021 she is mandated Chair of the GPOH Soft Tissue Sarcoma Study Group in Germany, Austria and Switzerland (former CWS Group including Sweden, Finland and Poland).

Martin Ebinger is a Consultant Pediatric Oncologist and Clinical Lead of the General Pediatric Oncology program at the University Children's Hospital in Tübingen. He is a board member of the Society for Pediatric Oncology and Hematology (GPOH), spokesperson for the University Center for Pediatric and Adolescent Oncology in Tübingen, and Co-Lead of the GPOH Soft Tissue Sarcoma Study Group (formerly CWS).

EpSSG MEMBERSHIP

EpSSG members represent Italy, UK, The Netherlands, France, Spain, Portugal, Belgium, Ireland, Denmark, Norway, Czech Republic, Croatia, Slovenia, Israel, Argentina, Brazil, Greece, Australia and Iran. In 2024, new members from the CWS group joined EpSSG. There were 174 individual members of the EpSSG from 20 different countries compared to 163 members in 2023.



EpSSG COMMITTEES

Chair

Biology	Dr. Michael Meister, Utrecht, The Netherlands
Pathology	Dr. Rita Alaggio, Rome, Italy
Imaging	Dr. Lise Borgwardt, Copenhagen, Denmark
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 and
	Dr Willemijn Breunis, Zurich, Switzerland

EpSSG MEETINGS 2024

The Spring meeting in 2024 took place in Milano, Italy during the 5th Annual Meeting of SIOP Europe. The EpSSG and Cooperative Weichteilsarkom Study group had a fruitful joint session regarding the present and future of non-rhabdo soft tissue sarcomas. In addition, surgeons and radiation oncologists of both groups participated in a local treatment session.
This has been a historical meeting for our Association as EpSSG became a Third Sector Entity during the Assembly with the attendance of a notary and our accountant.

The EpSSG Winter meeting was held in Paris (France) December 4th-6th.The local organizers were Lucy Metayer, Florent Guerin, Daniel Orbach, and Veronique Minard-Colin.
The discipline panel groups met at Gustave Roussy hospital on Wednesday 4th prior to the main Winter meeting. The main meeting took place at the Campus Les Cordeliers with 149 international delegates. The Campus des Cordeliers is a historic site located in the heart of Paris, in the 6th arrondissement, between Rue de l'École de Médecine and Boulevard Saint-Germain. Les Cordeliers is one of the emblematic places where the French Revolution was prepared.

There were very productive sessions on brachytherapy treatment, other local treatment and synovial Sarcoma. Prof. Hervé Fridman, professor Emeritus of Immunology at the University of Paris, gave an outstanding keynote lecture on Immunology.
At the Gala Dinner, held in Hotel Poulpry a special place to gather and chill after a full day of science. Lucy Metayer with Daniel Orbach have organized some quiz to continue the magic of the Olympic Games in Paris.

THE NEW FRONTLINE AND RELAPSE STUDY IN RHABDOMYOSARCOMA

(By Dr. Julia Chisholm on behalf of the CRCTU team)

Trial Update December 2024

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 four years and is recruiting well, with 797 patients registered so far. The CT3 relapse research question opened in March 2022, funded by Bayer. The phase 1b question completed recruitment in November 2023, and we are pleased to announce that the CT1a and CT1b induction chemotherapy randomisations subsequently opened in April 2024.

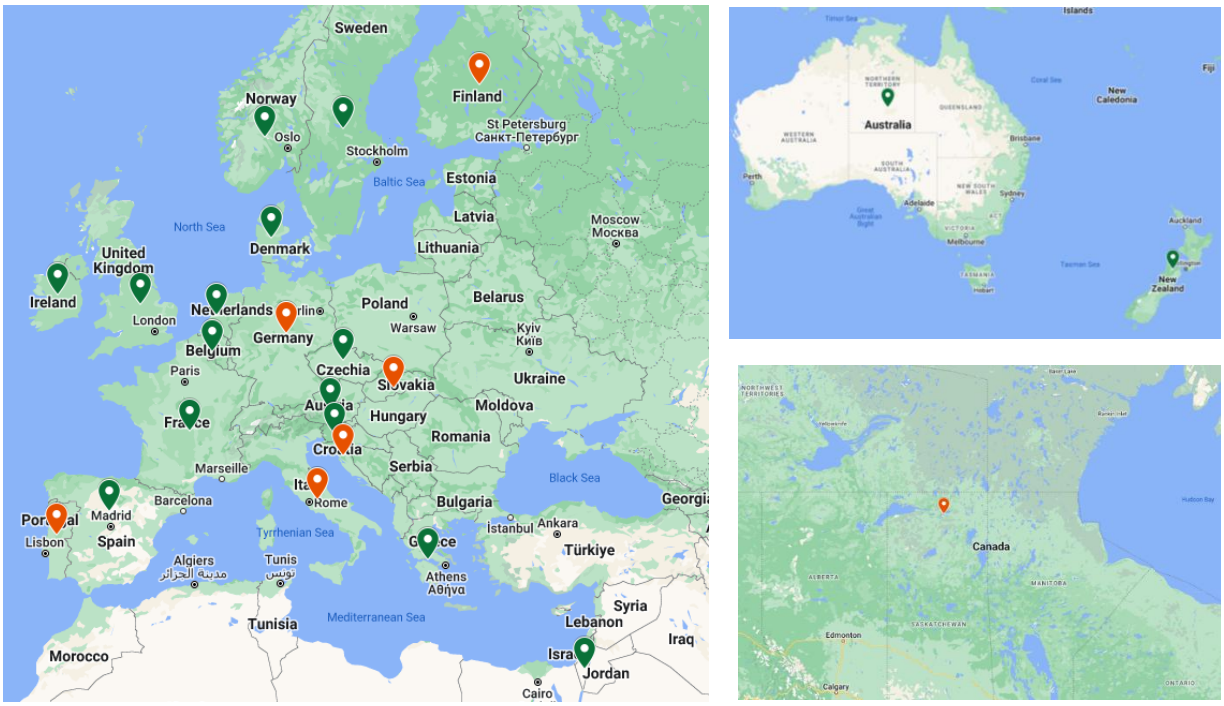
We are delighted that there is widespread international interest, and we continue to work with new countries to open the trial. The current recruiting countries are:

Country	**Number of open sites**
Australia	11
Austria	5
Belgium	7
Czech Republic	2
Denmark	2
France	36
Greece	7
Ireland	0
Israel	6
Netherlands	2
New Zealand	2
Norway	5
Slovenia	1
Spain	13

	Sweden	8
	Switzerland	9
	United Kingdom	28

Countries still in set-up since last update:
Canada, Croatia, Finland, Germany, Italy, Portugal, Slovakia, Singapore.

Open and Set-up Countries



Green = Countries Open Orange = Countries in Set-up

Phase 1b Dose Escalation Study – Recruitment Complete

The purpose of the Phase 1b question was to establish the dose of irinotecan in combination with ifosfamide, vincristine and actinomycin D. This question was open at ITCC and early phase approved centres. It completed recruitment in December 2023.
22 patients have been recruited to Phase 1b.

Induction Chemotherapy (CT1a/b)

Following the completion of Phase 1b, the CT1 randomisations opened on 10-Apr-2024 via a non-substantial protocol amendment. These questions compare the determined dose of irinotecan (50mg/m^2) in combination with ifosfamide, vincristine and actinomycin D, against the current standard of care for patients with High Risk and Very High Risk disease.
So far, 56 patients have been recruited to the CT1 induction questions.

Radiotherapy (RT1a/b/c, RT2)

All sites delivering radiotherapy are approved by QUARTET (Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials) and all radiotherapy plans for patients randomised to a radiotherapy question are prospectively reviewed by QUARTET. Prospective review aims to help standardise the radiotherapy being delivered within the FaR-RMS trial. The radiotherapy

randomisations are open to recruitment. The radiotherapy questions are pre vs post-operative radiotherapy (RT1a), dose-escalation in patients at higher risk of local failure (RT1b for patients with resectable disease, RT1c for non-resectable disease) and comparing limited vs extensive radiotherapy for patients with extensive metastatic disease (RT2). An important aspect of the study focusses on the Quality of Life of patients when receiving radiotherapy.
So far, 209 patients have been recruited to the Radiotherapy questions.

Maintenance Chemotherapy (CT2a/b)
The purpose of the CT2 questions is to extend the number of maintenance chemotherapy cycles for patients with HR and VHR disease compared to the current standard of care i.e. 6 vs 12 cycles and 12 vs 24 cycles respectively. Please note that some younger patients may not be able to swallow cyclophosphamide capsules. Where sites need access to oral liquid formulations, this should be discussed with the National Coordinating Centres.
So far, 149 patients have been recruited to the Maintenance questions.

Relapsed RMS (CT3)
The randomisation for patients with relapsed RMS (CT3) opened in March 2022. The first new combination to be tested is vincristine, irinotecan (VI) + regorafenib, a multi-tyrosine kinase inhibitor, vs VI + Temozolomide (VIT) as the control arm. The relapse study is an investigator-led collaboration between EpSSG and Bayer, the manufacturer of regorafenib. Quality of Life questionnaires are collected for all CT3 patients.
So far, 79 patients have been recruited to the CT3 question.

Pathology
Risk group assignment and fusion status are integral parts of the trial, and molecular diagnostics for all cases of RMS should be carried out at the local centre. All samples will be centrally reviewed in each country by the National Pathology Coordinator. An international review of scanned slides is ongoing with over 597 cases having undergone international review so far.

FDG-PET Sub-Study
If FDG PET-CT or FDG PET-MRI scanning is available at diagnosis & facilities allow, there is the option to take part in this sub study where an additional scan after 3 courses of induction chemotherapy is undertaken to determine the prognostic value of FDG-PET imaging response for EFS and local failure free survival. The collection of scans started in 2024 and is ongoing.

DW-MRI Sub-Study:
The aim of this sub-study is to investigate the prognostic value of DW-MRI imaging response 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. The collection of scans started in 2024 and is ongoing.

Quality of Life (QoL)
The Sarcoma Assessment Measure – Paediatrics (SAM-Paeds) is a QoL measure that was developed for teenage and adult patients. The SAM-Paeds measure will be added to the next version of the FAR-RMS protocol. The aim is to extend the Quality of Life study within FaR-RMS to correlate with a focus on the impact of local therapy (short- and longer-term outcomes). This will allow a more detailed understanding of the impact of local therapy for RMS for patients in the medium and long term. Currently, Quality of Life data is collected for patients entering RT1a, RT2 and CT3.

Surgery
This substudy will analyse the impact of surgery (as part of local control) on short term and late toxicity and Quality of Life. A surgical review of the data entry is ongoing.

Biology
This substudy will establish a virtual biobank for samples, including liquid biopsies, to evaluate prognostic factors at diagnosis, response to treatment and disease recurrence. The preferred storage of samples in is the VIVO biobank, Newcastle, UK, but some countries will use national biobanks.

Patient Videos
In collaboration with Alice's Arc, patient and parent representatives and Enfuse, a video is being developed to help prospective patients understand the study. Initially a video on the radiotherapy randomisations has been developed, with a FaR-RMS overview video additionally planned. The format of the videos will allow translation into other languages.
The patient video can be viewed on the FaR-RMS Website: Far-RMS - University of Birmingham

Vinorelbine Pharmacokinetic (PK) Study
Funding has been secured in Denmark to investigate the PK of IV and oral vinorelbine and explore opportunities for the use of oral vinorelbine within the FaR-RMS trial.

EU-CTR Transition
The European Union Clinical Trials Regulation (EU-CTR) was implemented on 31st January 2022 and the FaR-RMS trial was required to transition to the Clinical Trials Information System (CTIS) by 31st January 2025 for EU regulatory approvals to remain valid. The FaR-RMS trial successfully completed transition of 17 countries' ethical and competent authority approvals to the CTIS system on 15th November 2024.

Sponsor
The Study Sponsor is the University of Birmingham Cancer Research UK Clinical Trials Unit,
EudraCT Number: 2018-000515-24, EU CT number 2024-510579-40-00.

FaR-RMS
Frontline and Relapse
RhabdoMyoSarcoma study

PARENTS AND EpSSG 2024

(By Sara Wakeling, Delphine Heenen and Angelika Sandakly)

FOCUS ON PATIENT/PARENTS GROUP

The parent group comprises individuals across EpSSG countries (active parents come from France, 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. During this time period, the group has been involved in brainstorming and setting achievable priorities for the role of involving and engaging parents & patients within the EpSSG.
Below is a summary of ongoing and new activities.

1 -Involvement in clinical trials/Research

- **FaR-RMS Trial**
  - Attendance at the Trial Steering Group and Trial Management Group meetings .
  - Work to create a video explainer for the parent/patient community regarding the trial goals and experience from the patient perspective. This is being conducted by a collaboration of young cancer survivors at the Royal Marsden and parent-led rhabdomyosarcoma children's charity, Alice's Arc. This group are contributing to the script development, video style and character development. The goal is to ensure that this is accessible across multiple trial locations with multi-language versions available.
  - Provided advice on the key messaging, tone, style, information provision and language requirements in the creation of a video designed to explain the radiotherapy arm of the trial with a view to enhancing recruitment.

- **MyKids Trial** - Attendance at the Trial Steering Group meetings.

2 - PPI/E strategy setting

Following the Rome meeting in 2022, a plan was developed setting out goals for the role of the parent group within the EpSSG. One output was that parents are now part of the phase 1/2 clinical trial and newly-formed rhabdomyosarcoma discipline groups. They attend meetings bringing the parent perspective to the group.

3 - Alice's Arc funding

Alice's Arc, children's cancer charity focused on research into rhabdomyosarcoma, continues to provide funding for two roles within the EpSSG - Project Manager and Statistician. These roles aim to enhance the efficient running of the organisation and ensure that data generated from clinical trials such as RMS 2005 are analysed in order to inform new research and to publish across academic publications and relevant parent/patient platforms. The organisation also sponsored the first in-person meeting of the EpSSG Biology Committee in September 2024, at a workshop aiming to bring biologists together to discuss new directions of research, working with key funders in the area and laboratory updates.

4- The future

The voice of parents and patients is becoming increasingly recognised in the formation of patient-centric research questions. We will continue to 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

Parents involved in publications associated with EpSSG

Chisholm, J.; Mandeville, H.; Adams, M.; Minard-Collin, V.; Rogers, T.; Kelsey, A.; Shipley, J.; van Rijn, R.R.; de Vries, I.; van Ewijk, R.; et al. Frontline and Relapsed Rhabdomyosarcoma (FAR-RMS) Clinical Trial: A Report from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). *Cancers* **2024**, *16*, 998. https://doi.org/10.3390/cancers16050998

NEW STUDY PROPOSALS ARE WELCOME

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.

PAPERS IN 2024

1. Frontline and Relapsed Rhabdomyosarcoma (FAR-RMS) Clinical Trial: A Report from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). **Cancers (Basel). 2024** Feb 29;16(5):998. doi: 10.3390/cancers16050998.PMID: 38473359

Chisholm J.

This review article describes the rationale, design and study questions of the international EpSSG Frontline and Relapse Rhabdomyosarcoma Study (FaR-RMS), the currently open study in rhabdomyosarcoma. It is written by the discipline leads involved in the trial and coauthored by EpSSG parents who are providing very significant support to the trial. It is summarised as follows:

The Frontline and Relapsed Rhabdomyosarcoma (FaR-RMS) clinical trial is an overarching, multinational study for children and adults with rhabdomyosarcoma (RMS). The trial, developed by the European Soft Tissue Sarcoma Study Group (EpSSG), incorporates multiple different research questions within a multistage design with a focus on (i) novel regimens for poor prognostic subgroups, (ii) optimal duration of maintenance chemotherapy, and (iii) optimal use of radiotherapy for local control and widespread metastatic disease. Additional sub-studies focusing on biological risk stratification, use of imaging modalities, including [18F]FDG PET-CT and diffusion-weighted MRI imaging (DWI) as prognostic markers, and impact of therapy on quality of life are described. This paper forms part of a Special Issue on rhabdomyosarcoma and outlines the study background, rationale for randomisations and sub-studies, design, and plans for utilisation and dissemination of results.

2. Localized incompletely resected standard risk rhabdomyosarcoma in children and adolescents: Results from the European Paediatric Soft Tissue Sarcoma Study Group RMS 2005 trial. **Cancer 2024** Jul 26. doi: 10.1002/cncr.35497.

Mandeville HC,

This study evaluated the outcomes of children and young people with localised rhabdomyosarcoma affecting different areas including the eye, the genital/ urinary system, or head and neck areas that are not close to the bottom of the skull. These patients either did not have surgery as their first treatment, or if they had surgery still had some disease remaining.
A total of 359 patients were included. For patients having radiotherapy as part of their treatment, we showed that they could safely receive a lower intensity of one of their chemotherapy drugs (ifosfamide or cyclophosphamide), with 93.7% alive at 5 years. For all patients, the chance of being free of rhabdomyosarcoma at 5 years was better for those having radiotherapy; however, their chance of being alive at 5 years was not better. Patients with rhabdomyosarcoma affecting the eye did have a better chance of being alive at 5 years if they had radiotherapy (97.3%) compared to those who did not have radiotherapy (87.1%).
Finally, we reported the outcomes of 60 patients where their tumour was completely removed by surgeons after they had received chemotherapy, with nothing visible at the edges when the tumour was looked at under the microscope. Interestingly we found that the chance of this group of patients being free of rhabdomyosarcoma, or alive, at 5 years was not improved by having additional radiotherapy.

3. Brachytherapy for rhabdomyosarcoma: Survey of international clinical practice and development of guidelines. Radiother Oncol. 2024 Jun;195:110273. doi: 10.1016/j.radonc.2024.110273.

Dávila Fajardo R,

This study focused on improving the treatment of children with a type of cancer called rhabdomyosarcoma, using a special form of radiation called brachytherapy. Brachytherapy involves placing radioactive material directly inside or next to the tumor, allowing high-dose treatment to the cancer while sparing healthy tissue.
Until now, there has been very little information about how brachytherapy is used for children with this cancer. To address this, a group of international experts—including radiation doctors and surgeons—came together to share their experiences, review existing research, and fill out a detailed survey.
They found that brachytherapy is most commonly used after surgery to remove the tumor, but is also sometimes used on its own. A newer technique, called high-dose-rate (HDR) brachytherapy, is becoming more common, especially for tumors in the urinary or reproductive systems. The experts also discussed how to choose which patients should receive brachytherapy, how to plan and deliver the treatment, and how to report the dose given.

As a result of this collaboration, the team created new guidelines to help doctors around the world use brachytherapy more consistently and effectively in children with rhabdomyosarcoma. These guidelines are now being used in a major ongoing international study called FaR-RMS.

4. Indeterminate pulmonary nodules in non-rhabdomyosarcoma soft tissue sarcoma: A study of the European paediatric Soft Tissue Sarcoma Study Group. **Cancer 2024** Feb 15;130(4):597-608. doi: 10.1002/cncr.35061.

Giraudo C,
Radiologists should be aware of the classification of indeterminate pulmonary nodules in non-rhabdomyosarcoma soft tissue sarcomas and use it in their reports. More than a third of patients with non-rhabdomyosarcoma soft tissue sarcoma can be affected by indeterminate pulmonary nodules. Indeterminate pulmonary nodules do not significantly affect the overall survival of pediatric patients with non-rhabdomyosarcoma soft tissue sarcoma.

5. Reappraisal of prognostic factors used in the European Pediatric Soft Tissue Sarcoma Study Group RMS 2005 study for localized rhabdomyosarcoma to optimize risk stratification and generate a prognostic nomogram**. Cancer 2024** Jul 1;130(13):2351-2360. doi: 10.1002/cncr.35258.

De Salvo GL,
This study used data from patients enrolled in the EpSSG RMS 2005 study to investigate the role of traditional clinical factors together with FOXO1 fusion status in non-metastatic rhabdomyosarcoma with the aim to develop a predictive model for event-free survival and provide a rationale for risk stratification for future trials. The multivariable model retained 5 prognostic factors including age at diagnosis interacting with tumor size, tumor primary site, IRS group, and FOXO1 fusion status. Based on each patient's total score in the nomogram, patients were stratified into four groups. The 5-year EFS rates were 94.1%, 78.4%, 65.2%, and 52.1%, respectively, in low-, intermediate-, high-, and very high-risk groups. The corresponding 5-year OS rates were 97.2%, 91.5%, 74.3%, and 60.8%. The most important result is the replacement of histology with fusion status and this model was utilized for the patient stratification in the new FaR RMS trial.

6. Prognostic role of bone erosion in orbital RMS: a report from the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG). Front Oncol. 2024 Dec 12;14:1497193. doi:10.3389/fonc.2024.1497193. eCollection 2024.

Di Carlo D,
Orbital rhabdomyosarcoma (RMS) typically remains confined to the orbital cavity and has a favorable prognosis. However, when the tumor erodes the orbital bone, it may resemble parameningeal RMS (PM-RMS) and require more aggressive treatment. Current treatment protocols do not account for varying degrees of bone erosion (BE), which complicates risk classification and treatment decisions. To address this, we analyzed 199 patients with orbital RMS included in the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) protocol, categorizing BE into minimal (bone thinning), moderate (focal lysis), and extensive (complete cortical destruction). BE was observed in 27.6% of patients, with 13.6% classified as minimal, 3.5% as moderate, and 10.6% as extensive. Extensive BE was associated with larger tumors (>5 cm) and invasive characteristics. After a median follow-up of 70.4 months, 5-year event-free survival (EFS) and overall survival (OS) rates were 76% and 92%, respectively. Patients without BE had significantly better OS (95% vs. 81%) but not EFS. Extensive BE was associated with worse outcomes compared to no/minimal/moderate BE, with EFS of 57.1% vs. 78.1% and OS of 71.1% vs. 94%. Patients with extensive BE experienced more frequent relapses, particularly in the central nervous system or meninges. These findings suggest that only patients with orbital RMS and extensive BE should be classified as PM and treated with intensified protocols

NRSTS PROJECTS

(by Prof. Andrea Ferrari & Dr. Daniel Orbach)

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

The EpSSG NRSTS Committee has recently started its new biological study 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). First patient has been enrolled in The Netherland 31 May 2024. Activation of other countries is ongoing.

In parallel, the NRSTS Committee is working on two other prospective therapeutic projects: joining forces with the CWS group to develop:
a randomized phase II trial dedicated to pediatric desmoid-type fibromatosis, aiming to evaluate efficacy of new drugs and new combination of drugs in this tumor.

The REACH NRSTS project - REgorafenib in young adults, Adolescents and Children with High-risk NRSTS – exploring whether the addition of Regorafenib to standard IfosfamideDoxorubicine chemotherapy improve outcome in high-risk NRSTS (PIs – Susanne Gatz, Andrea Ferrari).

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 are ready to be analyzed to improve knowledge on such rare sarcomas. Projects will: -

- Analyze the nodal tumor spread presentation in pediatric NRSTS and the pattern of relapse according to the initial loco-regional therapy applied. This project aims to define the prognostic role of regional nodal involvement in NRSTS, develop recommendations for initial nodal exploration according to tumor histotype, discuss the need for systematic regional nodal radiotherapy in specific clinical presentations and analyze the outcome of patients with NRSTS with nodal regional extension
- Compare the response rate of patients after neoadjuvant chemotherapy vs chemo-radiotherapy
- Define the role of adjuvant therapy in large NRSTS and/or IRS II NRSTS

FINANCIAL STATEMENT 2024

(by Dr. T. Rogers, Prof. H. Merks)

An accountancy and treasurer's Report of the final year's account was presented and approved during the EpSSG Spring meeting Assembly held in May 15, 2025 during the 5th SIOPE Annual Meeting in Budapest.

The 2024 Financial Report has closed with a result of €11,184 and is composed of the balance sheet, management report, and mission statement, as required by Article 13 of Legislative Decree 117/2017. The report was prepared according to the accrual accounting principle and reconciled with the ordinary cash flows of the financial year. The Treasurer reminded those present of the consistency of the data compared to the previous year and highlights the ongoing and coherent trend related to general interest activities.

For 2025 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 2025: EpSSG will receive financial support from Alice's Arc Foundation to support our EpSSG scientific project manager and statistician for the year 2024 and 2025.

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.

WORK PLAN IN 2025

- Continue expanding the FaR-RMS study by opening it in countries and centers not yet participating.
- Promote patient and parent engagement in the randomized trial questions, with support from our parents' organization to ensure clear and accessible explanations for families.
- Strengthen and optimize participation in FaR-RMS substudies, including Imaging, Biology Biomarkers, and Quality of Life studies.
- Begin developing ideas and planning for the next RMS study, led by the RMS Working Group.
- Accelerate the launch and implementation of the MyKIDS study across EpSSG countries.
- Establish a new set of NRSTS studies (platform trial), coordinated by the NRSTS Working Group.

- Ensure efficient preparation of reports by the International Data Center (IDC), working closely with project PIs to support timely submission of manuscripts to peer-reviewed journals.
- Consolidate funding for the IDC and EpSSG secretariat, which are essential to the network's organization and capacity to produce scientific output.

Strengthen collaboration with parents by actively involving them in meetings and projects. Support the ongoing work of the EpSSG Discipline Panels to update practice guidelines, initiate key analyses, and identify priority questions for future prospective clinical trials. Organize our twice yearly EpSSG live meetings; first the spring at the SIOPE meeting in Budapest 2025.

CALENDAR 2024

DATE	MEETING	LOCATION	NOTES
2024			
May 13-17 (Mon-Fri)	EpSSG Spring Meeting & Association Assembly	SIOP Europe 2024 5th Annual Meeting Milano	Confirmed
December 5-6 (Thu-Fri)	EpSSG Winter Meeting & Association Assembly	Paris	Confirmed

CALENDAR 2025-2026

DATE	MEETING	LOCATION	NOTES
2025			
May 12-16 (Mon-Fri)	EpSSG Spring Meeting & Association Assembly	SIOP Europe 2025 6th Annual Meeting Budapest	Confirmed
December 3-5 (Wed-Fri)	EpSSG Winter Meeting & Association Assembly	Athens	Confirmed
2026			
May 4-8 (Mon-Fri)	EpSSG Spring Meeting & Association Assembly	SIOP Europe 2025 6th Annual Meeting Glasgow	Confirmed
December 2-4 (Wed-Fri)	EpSSG Winter Meeting & Association Assembly	Padova	Confirmed

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

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.

www.epssgassociation.it

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and with the great
collaboration of all
EpSSG Members