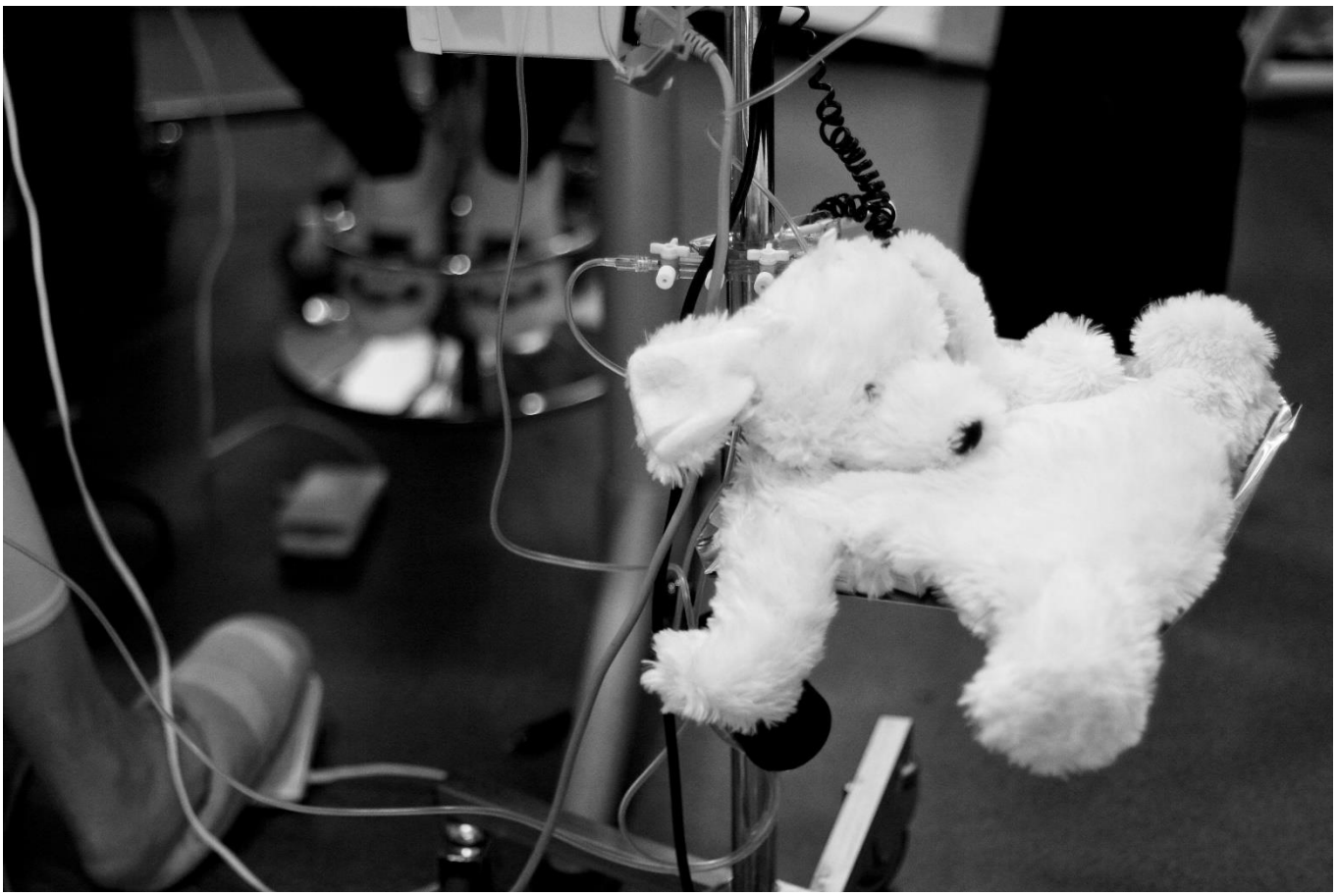
# ANNUAL REPORT 2023



# The European Paediatric Soft tissue sarcoma Study Group

# INDEX

# 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 or Adult-type 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 2023. 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

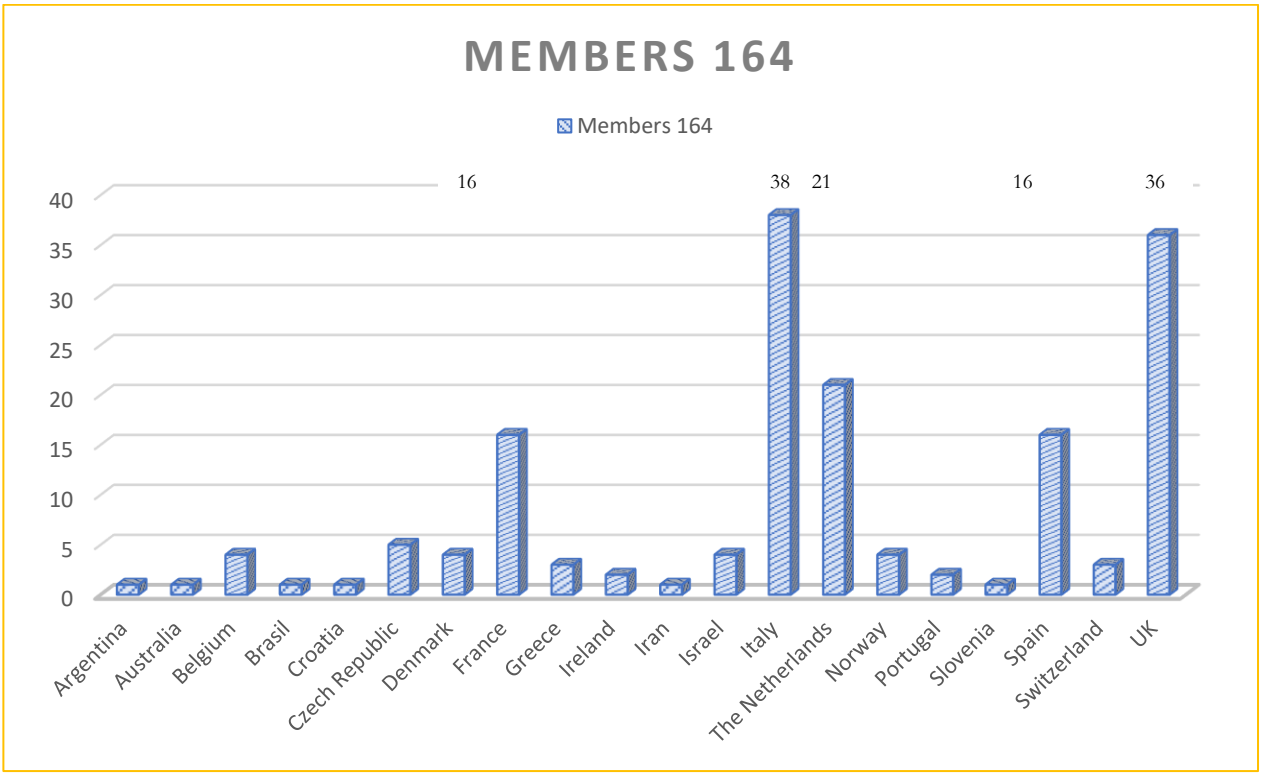
# EpSSG BOARD

| | |
|---|---|
| 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 |
| Dr. Andrea Ferrari | • Milan. Italy |
| Dr. Gabriela Guillén Burrieza | • Barcelona, Spain |
| Dr. Nadège Corradini | • Lyon, France |
| Dr. Lisa Hjalgrim | • Copenhagen, Denmark |

Board meetings were held remotely in 2023 each second Monday of the month: January 9th , February 13th, March 13th , April 10th, June 12st , July 10th, September 12nd , October 9th and November 13th . The board met in Valencia in May and Barcelona in December the day before the official meetings.

# EpSSG MEMBERSHIP

EpSSG members represent mostly: Italy, UK, The Netherlands, France, Spain, Portugal, Belgium, Ireland, Denmark, Norway, Czech Republic, Croatia, Slovenia, Israel, Argentina, Brazil, Greece, Australia and Iran. In 2023, there were 164 individual members of the EpSSG from 20 different countries compared to 158 members in 2022.




# 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 |

# EpSSG MEETINGS 2023

The Spring meeting in 2023 took place in Valencia (Spain) during the 4th Annual Meeting of SIOP Europe. The EpSSG and Cooperative Weichteilsarkom Study 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. A joint session between EpSSG and ITCC explored new drugs for patients with rhabdomyosarcoma.

The EpSSG Winter meeting was held in Barcelona (Spain) from November 29 until December 1st and was hosted by Vall d´Hebron University Hospital. The local organizing committee were Dr. Gabriela Guillen Burrieza, Dr. Raquel Hladun, Dr. Lucas Moreno and Dr. Josep Roma. The discipline panel groups met at Vall d´Hebron University Hospital on Wednesday 29th prior to the main Winter meeting. The main meeting took place during Thursday 30th and Friday 1st, with 139 international delegates. There were very productive sessions on maintenance treatment, poor risk RMS and INI-1 deficient tumors. Dr. César Serrano, from Vall d´Hebron Institut d´Oncologia (VHIO), gave the keynote lecture.
At the Gala Dinner, Professor Soledad Gallego, from Vall d´Hebron University Hospital, received a well-deserved tribute to her career and contributions to EpSSG.

# THE NEW FRONTLINE AND RELAPSE STUDY IN RHABDOMYOSARCOMA

**(BY PROF. MERIEL JENNEY AND DR. JULIA CHISHOLM on behalf of the CRCTU team)**

Trial Update December 2023

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.

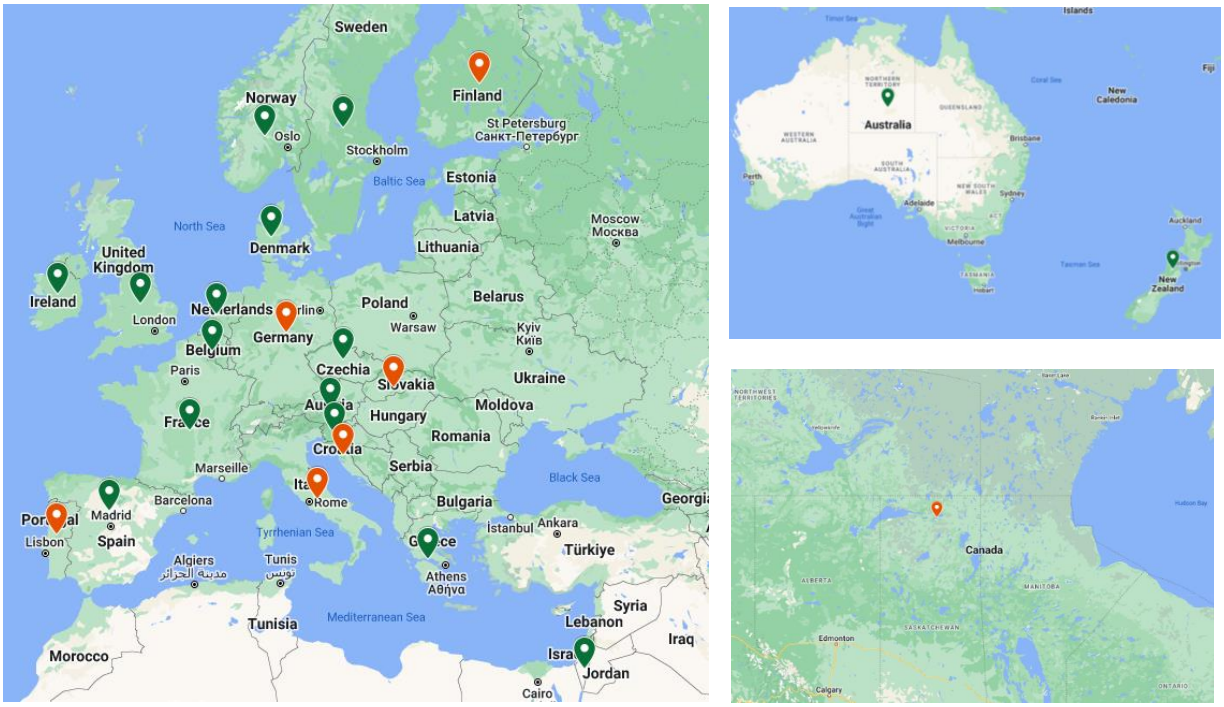
The trial has now been open for over three years. It is recruiting well and we are pleased to announce the relapse research question opened in March 2022, funded by Bayer. The phase 1b question completed recruitment in November 2023.

We are delighted that there is wide international interest, and that in the last year, several new countries have opened the trial. The current recruiting countries are:

| **Country** | **Number of open sites** |
|---|---|
| Australia | 11 |
| Austria | 1 |
| Belgium | 7 |
| Czech Republic | 2 |
| Denmark | 2 |
| France | 25 |
| Greece | 8 |
| Ireland | 0 |
| Israel | 6 |
| Netherlands | 2 |
| New Zealand | 2 |
| Norway | 5 |
| Slovenia | 1 |
| Spain | 10 |
| Sweden | 2 |
| Switzerland | 10 |
| United Kingdom | 28 |

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

**Open and Set-up Countries**




**Green = Countries Open Orange = Countries in Set-up**

**Phase 1b Dose Escalation Study** – recruitment complete.
To find the dose of irinotecan in combination with ifosfamide, vincristine and actinomycin-D. This question was open at ITCC and early phase approved centres. It has now completed recruitment.
**21 patients have been recruited to Phase 1b.**

**Induction Chemotherapy (CT1a/b)**
The CT1 randomisations will open at all participating centres, upon completion of the Phase 1b question. These questions will compare the determined dose of irinotecan in combination with ifosfamide, vincristine and actinomycin-D, against the current standard of care for patients with High Risk and Very High Risk disease.

**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 randomized 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 postoperative radiotherapy (RT1a), dose-escalation in patients at higher risk of local failure (RT1b for patients with resectable disease, RT1c for non-resectable) 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, 106 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 centres need access to oral liquid formulations, this should be discussed with the National Coordinating Centres.

So far, 80 patients have been recruited to the Maintenance questions.

**Relapse RMS (CT3)**

The randomisation for patients with relapsed RMS opened in March 2022. The first new combination to be tested is vincristine, irinotecan (VI) + regorafenib, a multityrosine 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, 26 patients have been recruited to the CT3 question.

**Pathology**

Risk group assignment and fusion status are integral part of the trial, 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 292 cases having international review.

**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 will be started in 2024.

**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 will be started in 2024.

**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 SAM-Paeds measure has been designed and is in the process of validation. The FaR-RMS study provides a unique platform to understand better the experience of patients of all ages, and their families. The aim is 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 for patients in the medium and long term. Currently quality of life data is collected for patients entering RT1a, RT2 and CT3.

**Surgery**

Impact of surgery (as part of local control) on short term and late toxicity and QoL. A surgical review of the data entry has recently stated.

**Biology**
To 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 is planned, with a FaR-RMS overview video additionally planned. The format of the videos will allow translation into other languages.

**Vinorelbine Pharmacokinetic (PK) Study**
To investigate the PK of IV and oral vinorelbine and explore opportunities for the more extensive use of oral vinorelbine within the FaR-RMS trial.

**EU-CTR**
The deadline to transfer all open clinical trials in the EU to the Clinical Trials Information System is 31-Jan-2025. FaR-RMS is planned to be transferred in Summer 2024.

**Sponsor**
The Study Sponsor is the University of Birmingham Cancer Research Clinical Trials, UK EudraCT Number: 2018-000515-24

# PARENTS AND EpSSG 2023

**(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.
  - Working to devise a pilot animation to help enhance recruitment of the radiotherapy arm of the FaR-RMS trial. This has been done in conjunction with trial leads and by engaging a PPI group via Alice's Arc.

- **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 - Developing a parent section on the EpSSG Website

The newly-launched EpSSG website now comprises a parent-focused page on the website. This provides those impacted by paediatric sarcoma with an overview about the group, news and user-friendly information regarding paediatric sarcoma and clinical trial data. Parents will seek feedback via their charitable organisations to ensure it is helpful.

### 4 - 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.

### 5- 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!

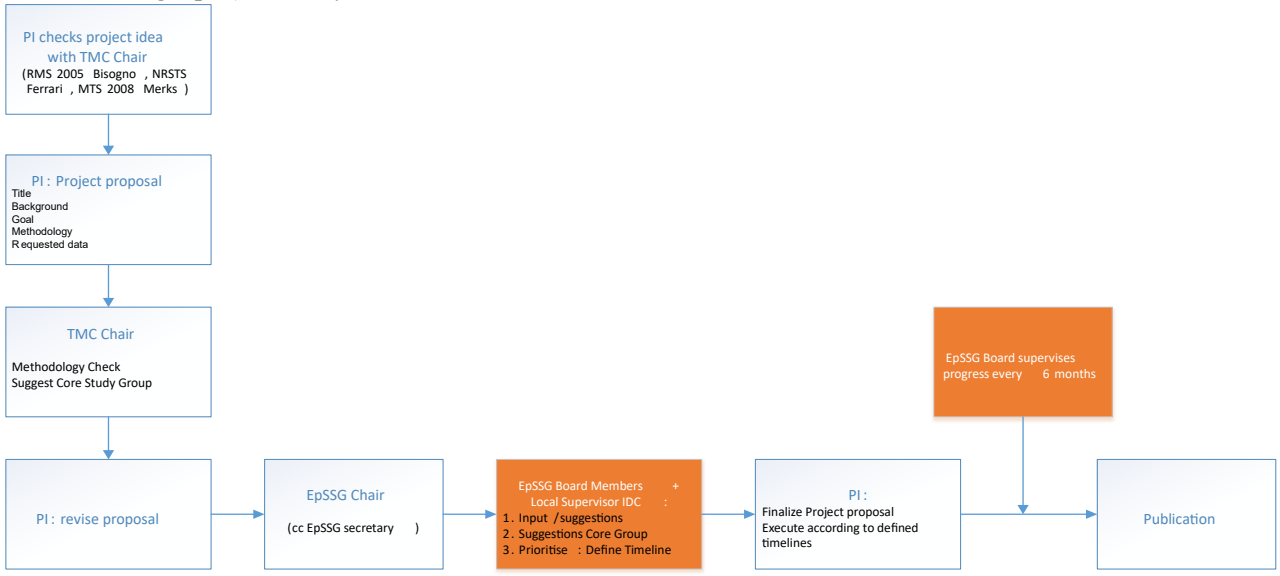
## Parents involved in publications associated with EpSSG

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

van Gorp, M.; Grootenhuis, M.A.; Darlington, A.-S.; Wakeling, S.; Jenney, M.; Merks, J.H.M.; Hjalgrim, L.L.; Adams, M. Patient Reported Outcomes and Measures in Children with Rhabdomyosarcoma. *Cancers* **2023**, *15*, 420. https://doi.org/10.3390/cancers15020420

## 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. In particular, a scheme is reported below. This explains the steps every PI should take before starting a project/analyses.



# PAPERS IN 2023


1. **Milano GM**, Orbach D, Casanova M, Berlanga P, Schoot RA, Corradini N, Brennan B, Ramirez-Villar GL, Lyngsie Hjalgrim L, van Noesel MM, Alaggio R, Ferrari A.
   **Malignant ectomesenchymoma in children: The European pediatric Soft tissue sarcoma Study Group experience.** Pediatr Blood Cancer. **2023 Feb;**70(2):e30116. doi: 10.1002/pbc.30116. Epub 2022 Nov 28.

This is a short report on 10 cases of malignant ectomesenchymoma (MEM) enrolled in the EpSSG NRSTS 2005 protocol (0.8% of the cases). MEM is an extremely rare soft tissue tumor typical of young children (often arising at genito-urinary sites), currently included in the category of skeletal muscle malignancies and characterized by a neuroblastic component. Of the 10 cases, 7 had an initial local diagnosis of rhabdomyosarcoma.

All patients received chemotherapy according to rhabdomyosarcoma strategy, four had radiotherapy. Overall, six patients were alive in first remission, two in second remission and one after second tumor. Only the patient with initially metastatic tumor died of disease.

More in-depth molecular investigations are needed to better study MEM tumorigenesis and its biphenotypic differentiation. Meanwhile, EpSSG proposes to treat these patients according to the RMS therapeutic strategy.

2. **Mercolini F**, Merks JHM, Minard-Colin V, Cameron A, van Scheltinga SEJT, Sher O, Fichera G, Orbach D, Glosli H, Coppadoro B, Gallego S, Chisholm JC, Bisogno G.
   **Metastatic rhabdomyosarcoma with exclusive distant lymph node involvement: A European Pediatric Soft tissue sarcoma Study Group (EpSSG) report.**
   Pediatr Blood Cancer. **2023 Mar**;70(3):e30143. doi: 10.1002/pbc.30143. Epub 2022 Dec 15.

"Prognosis of patients with metastatic rhabdomyosarcoma is still poor. However, efforts must be made to to stratify patients so that to tailor treatments.
In this study, patients affected by rhabdomyosarcoma with the presence of metastases to distant lymph nodes, in the absence of other metastatic sites of disease, were analysed. These patients have been found to have markedly superior prognoses to other patients with metastatic disease and comparable to those with localized disease and locoregional lymph node involvement. In particular patients with fusion-negative (PAX3/7-FOXO1) tumors showed excellent prognosis.
This data, which will have to be confirmed on even larger series, could suggest that some rhabdomyosarcomas may have a tendency to spread exclusively by lymphatic route (and not by hematogenous route) and present a minor biological aggressiveness.

3. Bisogno G, Minard-Colin V, Zanetti I, Ferrari A, Gallego S, Davila Fajardo R, Mandeville H, Kelsey A, Alaggio R, Orbach D, Terwisscha van Scheltinga S, Guillen Burrieza G, Ben-Arush M, Glosli H, Mudry P, Ferman S, Devalck C, Defachelles AS, Merks JHM, Jenney M. **Nonmetastatic Rhabdomyosarcoma in Children and Adolescents: Overall Results of the European Pediatric Soft Tissue Sarcoma Study Group RMS2005 Study.** J Clin Oncol 2023 May 1;41(13):2342-2349.doi: 10.1200/JCO.22.02093. Epub 2023 Feb 27.

**Purpose**: This reports the results of the nonmetastatic group of 1733 patients enrolled on the RMS2005 study. It also analyses the evolution of treatment in comparison with previous European protocols.
The RMS2005 study (co-ordinated by the EpSSG) was dedicated to children and adolescents aged 0-25 years old. It was open from October 1st, 2005, to December 31st, 2016. It included two phase III randomised trials for high-risk (HR) and observational trials for low (LR), standard (SR) and very high-risk (VHR) patients who have been partially reported.

**Results** (after a median follow-up of 73.1 months):

- 5-year event free survival (EFS) and overall survival (OS) were 70.7% and 80.4% respectively.
- By subgroup
    - LR (80 patients) – EFS 93.7% and OS 96.7%. Can be treated with relatively short, low-toxic chemotherapy.
    - SR (652 patients) – EFS 77.4% and OS 90.6%.
    - HR (851 patients) – EFS 67.3% and OS 76.7% (287 patients had an event and 212 died)
    - VHR (150 patients) – EFS 48.8% and OS 49.7% (77 patients had an event and 71 died)
- RMS2005 demonstrated that 80% of children with localised disease could be long term survivors. This relates to the excellent outcomes in the LR and SR groups.
- RMS2005 has established the standard of care across European (EpSSG) countries confirming a 22-week Vincristine/Actinomycin D regimen for LR patients, reduction of the cumulative ifosfamide dose in the SR group compared with previous European studies and the omission of doxorubicin and the addition of maintenance for the HR group.
- The Children's Oncology Group (COG) has a similar treatment duration for the LR group – 24 weeks, but this includes alkylating agents. The LR group for COG use cyclophosphamide instead of ifosfamide and the number of cycles is higher (16 for COG v nine for EpSSG)
- Broad overlap between patients included in the intermediate risk group by COG and EpSSG HR. COG provides VAC +/- irinotecan and EFS was 59-63% with a longer duration of chemotherapy (42 v 27 weeks in RMS2005)
- Patients with alveolar and regional lymph node involvement are at a very high risk of failure. 3-year EFS was 25% in the CWS-86 Study and 31% in the SIOP-MMT84 study. In the IRS-IV study the 5-year failure free survival was 43%. RMS2005 results showed improved results compared with previous European experiences but the outcome is still unsatisfactory.

4. Berlanga P, Orbach D, Schoot RA, Casanova M, Alaggio R, Corradini N, Brennan B, Ramirez-Villar GL, Hjalgrim L, Chisholm J, Bisogno G, Coppadoro B, Safwat A, Merks JHM, Guillen Burrieza G, van Noesel MM, Ferrari A. **Intra-abdominal desmoplastic small round cell tumor: The European pediatric Soft tissue sarcoma Study Group (EpSSG) experience.** Pediatr Blood Cancer 2023 May 26;e30447. doi: 10.1002/pbc.30447. Online ahead of print.

Desmoplastic small round cell tumor (DSRCT) is an ultra-rare and aggressive mesenchymal tumor characterized by the specific chromosomal translocation t(11:22)(p13;q12), which involves the EWS-WT1 fusion gene. It generally occurs in the peritoneal cavity of adolescent and young adult males, with advanced stage including large masses, multiple nodules in the peritoneal cavity, and extensive peritoneal seeding. Patients with DSRCT generally have a very poor prognosis, despite various intensive multi-modal treatments.
This study describes the clinical findings of a series of 32 patients aged less than 21 years (median age 13.7 years) with a diagnosis of DSRCT arising in the abdomen, prospectively enrolled in EpSSG protocols: the BERNIE study, the EpSSG MTS 2008 study, and the EpSSG NRSTS 2005 study. All trials recommended a multimodal approach including intensive multidrug chemotherapy and loco-regional treatment with surgery and/or radiotherapy whenever possible.
Three patients had localized tumors, seven had regionally disseminated disease, and 22 extraperitoneal metastases. All but one patient received multidrug chemotherapy and 11 had maintenance chemotherapy. Loco-regional treatment consisted of surgery only in seven cases, surgery plus adjuvant radiotherapy in 10, and radiotherapy only in six. Among the 17 cases who had radiotherapy, six had irradiation of the primary site, 10 had whole abdominopelvic radiotherapy plus boost to macroscopic residual disease, and one had irradiation to lung metastases only.
With a median follow-up of 76 months (range: 18–124 months), 5-year event-free and overall survivals were 19.7% and 21.0%, respectively. Event-free survival was significantly worse for patients who did not receive loco-regional treatment (p-value .007).
The study confirmed that the outcome of patients with DSRCT remains dismal and did not improve over recent years despite an intensive multimodal treatment approach. The management of young patients with DSRCT remains a major challenge. Different novel approaches, driven by preclinical models, are urgently needed, as well as wider collaborative research and cooperation on clinical trial design.

**5.** Ferrari A, Orbach D, Casanova D, van Noesel M M, Berlanga P, Brennan B, Corradini N, Schoot RA, Ramirez-Villar GA, Hjalgrim LL, Alaggio R, Guillen Burrieza G, Safwat A, Cameron A, van Rijn RR, Minard-Colin V, Zanetti I, Bisogno G, Chisholm J, Merks JHM. **Metastatic adult-type non-rhabdomyosarcoma soft tissue sarcomas in children and adolescents: A cohort study from the European paediatric Soft tissue sarcoma Study Group.** Cancer 2023 Apr 21. doi: 10.1002/cncr.34814. Online ahead of print

Pediatric non-rhabdomyosarcoma soft tissue sarcomas form a heterogeneous group of rare tumors. While recent international studies have defined the standard of care for patients with localized disease, limited data are available on the clinical behavior of patients with distant metastases at onset.
This study reports on 61 patients <21 years old with adult-type metastatic NRSTS enrolled from July 2008 to December 2016 in two concurrent prospective EpSSG studies, i.e. the randomized BERNIE study and the single-arm MTS 2008 study. Treatment programs were originally designed for patients with metastatic rhabdomyosarcoma, i.e. nine courses of multidrug chemotherapy (with or without bevacizumab in the BERNIE study), followed by twelve cycles of maintenance therapy, while

radiotherapy and/or surgery (on primary tumor and/or metastases) were delayed until after seven courses of chemotherapy had

All patients received multi-agent chemotherapy, 44% had local therapy to primary tumor, and 18% had treatment of metastases. Median time to progression/relapse was 6 months. A high rate of tumor progression was observed during the initial part of the chemotherapy program. With a median follow-up of 41.5 months (range 2-111 months), 3-year event-free survival and overall survival were 15.4% (95% CI 7.6-25.7) and 34.9% (95% CI 22.7-47.5), respectively. There were no statistically significant differences in outcome depending on the type of treatment administered.

The study confirmed the overall poor outcome for patients with metastatic NRSTS, whose treatment remains a challenge. Together with the subgroup of 80 metastatic patients enrolled in the COG ARST0332 study, this series may represent the reference for this disease category, and serve as the starting point for developing future dedicated investigational trials.

**6.** Guérin F, Martelli H, Rogers T, Zanetti I, van Scheltinga ST, De Corti F, Guillen Burrieza G, Minard-Colin V, Orbach D, van Noesel MM, Karanian M, Dávila Fajardo R, Merks JHM, Ferrari A, Bisogno G. **Outcome of patients with undifferentiated embryonal sarcoma of the liver treated according to European Soft Tissue Sarcoma protocols.** Pediatr Blood Cancer. 2023 Jul;70(7):e30374. doi: 10.1002/pbc.30374. Epub 2023 Apr 21.

Neoadjuvant chemotherapy for pediatric patients with UESL increases the quality of surgery.
Five-year overall and event-free survivals were 90.1% and 89.1% respectively.
Alkylating agents should not be omitted or reduced.
The role of anthracyclines and radiotherapy for localized disease remains unclear.

Lay summary: Our study assessed the outcomes of 65 pediatric patients with Undifferentiated Embryonal Sarcoma of the Liver treated according to successive European malignant mesenchymal tumor trials. This study demonstrated excellent outcomes with 90% overall survival and 89% event free-survival at 5 years with an association of chemotherapy and surgery. Neoadjuvant chemotherapy improved the quality of surgery. Eight events consisted of 4 local (2 were associated with invaded surgical margins), 3 metastatic relapses (two were associated with a reduced alkylating regimen), and one-second tumor. There was no statistical association between invaded margins, use of radiotherapy or anthracycline and these events.

**7.** Bisogno G, De Salvo GL, Minard-Colin V, Davila Fajardo R, Coppadoro B, Jenney M, Ferrari A, Hladun Alvaro R, Dall'Igna P, Glosli H, Merks JHM. **Time to broaden the eligibility criteria in paediatric oncology trials? An analysis of patients with rhabdomyosarcoma non-eligible to the EpSSG RMS2005** trialEJC. 2023 May doi: https://doi.org/10.1016/j.ejcped.2023.100014

Clinical trials for pediatric rhabdomyosarcoma (RMS) include specific rules to ensure patient safety and reduce variability. However, it's not clear how children who don't meet these rules fare. This study looked at the eligibility criteria used in the European paediatric Soft Tissue Sarcoma Study Group RMS2005 trial and compared the outcomes of patients who didn't qualify for the trial.

Between October 2005 and December 2016, the RMS2005 trial had strict rules: patients had to be 25 or younger, have confirmed RMS without metastases, have not received prior treatment, and had to start treatment within 8 weeks of diagnosis. The study examined the clinical details and survival rates of both eligible and non-eligible patients.

Out of the patients registered, 79 did not meet the eligibility criteria. These non-eligible patients were generally older and had RMS in less challenging locations, with their tumors fully removed at diagnosis. Their 5-year progression-free survival (PFS) and overall survival (OS) rates were slightly lower compared to eligible patients, but not significantly so. Notably, those who had delays in starting treatment or had been pre-treated fared better than those with existing conditions.

The findings suggest that data on non-eligible patients should be systematically gathered. This approach might help adjust trial criteria to improve patient inclusion without compromising the results, potentially enhancing the applicability of the findings to a broader population.

8. Chisholm JC, Schoot RA, Cameron AL, Casanova M, Minard-Colin V, Coppadoro B, Garrido B, Rogers B, Orbach D, Glosli H, Ben-Arush M, Ferman S, Scarzello G, van Rijn RR, Hladun R, Corradini N, Ferrari A, Jenney M, Bisogno G, Merks JHM. **Outcomes in lung-only metastatic rhabdomyosarcoma: An analysis of data from the European paediatric Soft tissue sarcoma Study Group MTS 2008 study** EJC 2023. https://doi.org/10.1016/j.ejcped.2023.100018

Among patients with metastatic rhabdomyosarcoma, outcomes are better in patients for whom lung is the only metastatic site. Oberlin has also identified 4 risk factors that are associated with adverse outcomes in metastatic rhabdomyosarcoma. This study reported on the clinical features, management and outcomes by Oberlin risk factors and use of lung radiotherapy in patients with lung-only metastatic rhabdomyosarcoma treated within the EpSSG MTS 2008 study.
Fifty nine patients with lung-only metastatic disease were identified among 270 registered in the MTS 2008 study. Their 3-yr Event Free Survival (EFS) was 40% (95%CI 27-53%) and 3-yr Overall Survival (OS) was 60% (95%CI 46-71%), better than published outcomes for the whole MTS 2008 group (3-year EFS 35%, OS 48%) . OS was significantly improved compared to patients with lung + other metastatic sites or other metastatic sites but outcomes did not differ between these groups when adjusted for known Oberlin risk factors. Radiotherapy to the lungs appeared to improve 3-year EFS but not OS (EFS: RT 56%, 95%CI 35-73% versus no RT 33%, 95%CI 16-52%, p= 0.0435. OS: 73%, 95%CI 51-86% versus 58%, 95%CI 36-75%; p=0.2048.
Overall it was concluded that better OS in lung-only MTS RMS is associated with fewer Oberlin risk factors and radiotherapy to the lung is recommended for patients with lung-only metastatic rhabdomyosarcoma.

9. Bisogno G, Minard-Colin V, Jenney M, Ferrari A, Chisholm J, Di Carlo D, Hjalgrim LL, Orbach D, Merks JHM, Casanova M **Maintenance Chemotherapy for Patients with Rhabdomyosarcoma.** Cancers (Basel). 2023 Aug 7;15(15):4012. doi: 10.3390/cancers15154012.

The updated results of the RMS2005 randomized study confirm that patients with non-metastatic high risk rhabdomyosarcoma have an improved survival when maintenance chemotherapy (MC) with vinorelbine and low dose cyclophosphamide is added to the standard multidisciplinary treatment. A

more recent randomized study adopted the same strategy, but different drugs were used in the MC phase (trofosfamide, idarubicin and etoposide). No survival improvement was evident in the MC group, suggesting that not all types of MC are equally effective. A revision of the literature demonstrates that the role of MC in patients with metastatic or relapsed RMS may be a promising approach but need more investigations.

Maintenance chemotherapy (MC) involves giving a less intense, prolonged course of chemotherapy to keep cancer in remission after the initial treatment. This update from the RMS2005 trial shows that adding MC with vinorelbine and low-dose cyclophosphamide to standard treatment improves survival for patients with high-risk localized rhabdomyosarcoma (RMS).
In the RMS2005 study, patients who received MC had a 5-year disease-free survival rate of 78.1%, compared to 70.1% for those who didn't receive MC. Their overall survival rate was also better: 85.0% versus 72.4%.
While there are several studies on MC in RMS, only one randomized trial looked at a different MC regimen and didn't find any benefit. However, non-randomized studies suggest that MC can be more effective and tolerable compared to high-dose chemotherapy, especially for patients with metastatic RMS or those who relapse.
There is still a lot to learn about the best drugs and treatment duration for MC in RMS. The ongoing EpSSG trial aims to answer these questions and refine MC treatment strategies.

**10.** Di Carlo D, Chisholm J, Kelsey A, Alaggio R, Bisogno G, Minard-Colin V, Jenney M, Dávila Fajardo R, Merks JHM, Shipley JM, Selfe JL **Biological Role and Clinical Implications of *MYOD1L122R* Mutation in Rhabdomyosarcoma.** Cancers (Basel). 2023 Mar 7;15(6):1644. doi: 10.3390/cancers15061644.

Recent advances have greatly improved our understanding of rhabdomyosarcoma (RMS), a type of cancer, helping us tailor treatments based on risk factors. In earlier studies, risk was determined solely by clinical factors. The latest European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) protocol, known as FaR-RMS, now includes genetic factors like the FOXO1 fusion gene status in assessing risk, instead of just relying on histology.

New research has identified additional important genetic features, such as the MYOD1L122R gene mutation. This mutation blocks cell differentiation and behaves similarly to the MYC gene, which is linked to more aggressive cancer behavior. MYOD1L122R often occurs alongside other mutations, like PIK3CA, suggesting these mutations might work together to drive the disease.

A review of ten studies involving 72 cases found that the MYOD1L122R mutation is present in both adults and children with RMS. It is commonly seen in specific tumor types, especially in the head, neck, and limbs, and is associated with poorer outcomes. This raises important questions about how to incorporate MYOD1L122R into risk assessments and the most effective ways to treat patients with this mutation.

**11.** van Ewijk R, Chatziantoniou C, Adams M, Bertolini P, Bisogno G, Bouhamama A, Caro-Dominguez P, Charon V, Coma A, Dandis R, Devalck C, De Donno G, Ferrari A, Fiocco M, Gallego S, Giraudo C, Glosli H, Ter Horst SAJ, Jenney M, Klein WM, Leemans A, Leseur J, Mandeville HC, McHugh K, Merks JHM, Minard-Colin V, Moalla S, Morosi C, Orbach D, Ording Muller LS, Pace E, Di Paolo PL, Perruccio K, Quaglietta L, Renard M, van Rijn RR, Ruggiero A, Sirvent SI, De Luca A, Schoot RA. **Quantitative diffusion-weighted MRI response assessment in rhabdomyosarcoma: an international retrospective study on behalf of the European paediatric Soft tissue sarcoma Study Group Imaging Committee.** Pediatr Radiol. 2023 Nov;53(12):2539-2551. doi: 10.1007/s00247-023-05745-z. Epub 2023 Sep 8.PMID: 37682330

This manuscript reports on a multicenter retrospective study including pediatric, adolescent and young adult patients with rhabdomyosarcoma, IRS group III/IV, treated according to the EpSSG RMS 2005 or MTS 2008 study. DW-MRI scans were performed according to institutional protocols. Two-dimensional single-slice tumor delineation was performed by experienced radiologists. Areas of necrosis or hemorrhage were delineated to be excluded in the primary analysis. Mean, median, 5th and 95th apparent diffusion coefficient (ADC) were extracted. In total 268 scans of 134 pediatric patients from 7 countries were enrolled (Belgium 10 patients; France 16; Italy 36; Norway 12; Spain 10; The Netherlands 46; United Kingdom 4). Median age was 6.0 years (range 0.3-21.8). Almost three-quarters of the patients had an embryonal rhabdomyosarcoma, nearly a quarter an alveolar rhabdomyosarcoma. Of 134 included patients, 82 had measurable tumor at diagnosis and response with sufficient quality of DW-MRI available and were included in the analysis. Technical heterogeneity in scan acquisition protocols and scanners was observed. Mean ADC at diagnosis was 1.1 [95% CI: 1.1-1.2] [all ADC expressed in * 10-3mm2/s], versus 1.6 [1.5-1.6] at response assessment. The 5th percentile ADC was 0.8 [0.7-0.9] at diagnosis and 1.1 [1.0-1.2] at response. Absolute change in mean ADC after neo-adjuvant chemotherapy was 0.4 [0.3-0.5]. Exploratory analyses for association between ADC and clinical parameters showed a significant difference of mean ADC at diagnosis for alveolar versus embryonal histology. Landmark analysis at 9 weeks after the date of diagnosis showed no significant association (Hazard ratio 1.3 (0.6-3.2)) between the mean ADC change and event-free survival in this heterogeneous cohort.
In conclusion, a significant change in the 5th percentile and the mean ADC after chemotherapy was observed. Strong heterogeneity was identified in DW-MRI acquisition protocols between centers and in the individual patient.

## COLLABORATION WITH OTHER GROUPS:

11. **Sparber-Sauer** M, Ferrari A, Spunt SL, Vokuhl C, Casey D, Lautz TB, Meyer WH, Walterhouse DO, Pajtler KW, Alaggio R, Schmidt A, Safwat A, Timmermann B, Dall'Igna P, Chen S, Weiss AR, Orbach D. **The significance of margins in pediatric Non-Rhabdomyosarcoma soft tissue sarcomas: Consensus on surgical margin definition harmonization from the INternational Soft Tissue SaRcoma ConsorTium (INSTRuCT)** . 2023 Feb 6. doi: 10.1002/cam4.5671. Online ahead of print.

# NRSTS PROJECTS

**(by Dr. 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 2023

**(by T. Rogers, 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 11, 2023 during the 4th SIOPE Annual Meeting in Valencia.Total income for the association in 2022 was €60.413,40, mainly from members' fees, meeting registration and donations from Alice's Arc.
Total expenses were almost €65.746,35.

For 2023 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 2023: EpSSG will receive financial support from Alice's Arc Foundation to support our EpSSG scientific project manager and statistician for the year 2023 and 2024.

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 2024

Continue to open the FaR-RMS study in countries and centers not open yet. Promote patient and parent participation in the randomized trial questions; this includes support from our parents organization to optimize explanation of these questions to patients and parents.
Implement and optimize participation in substudies to FaR-RMS including Imaging and Biology Biomarker studies and studies on Quality of Life
Open the MyKIDS Study and initiate the study across EpSSG countries.
Efficient preparation of reports by the International Data Center (IDC) in close collaboration with PI of each project leading to timely delivery of manuscripts to be published in peer reviewed journals.
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.
Continue the good work of the EpSSG Discipline Panels to deliver and update practice guidelines, initiate important analyses and new research.

Together with Dr Monika Sparber-Sauer and Prof Martin Ebbinger, chair and co-chair of CWS, we will explore to further intensify European collaboration, potentially aiming for integration.
Have our twice yearly EpSSG live meetings; first the spring at the SIOPE meeting in Milan 2024. In Milan we aim at changing our statutes and become a Third Sector Entity . Amongst others this may increase the associations income through a 5 pro mille code. The EpSSG Winter meeting will be organized by the Gustave Roussy Institute gently coordinated by Prof. Veronique Minard-Colin in Paris.

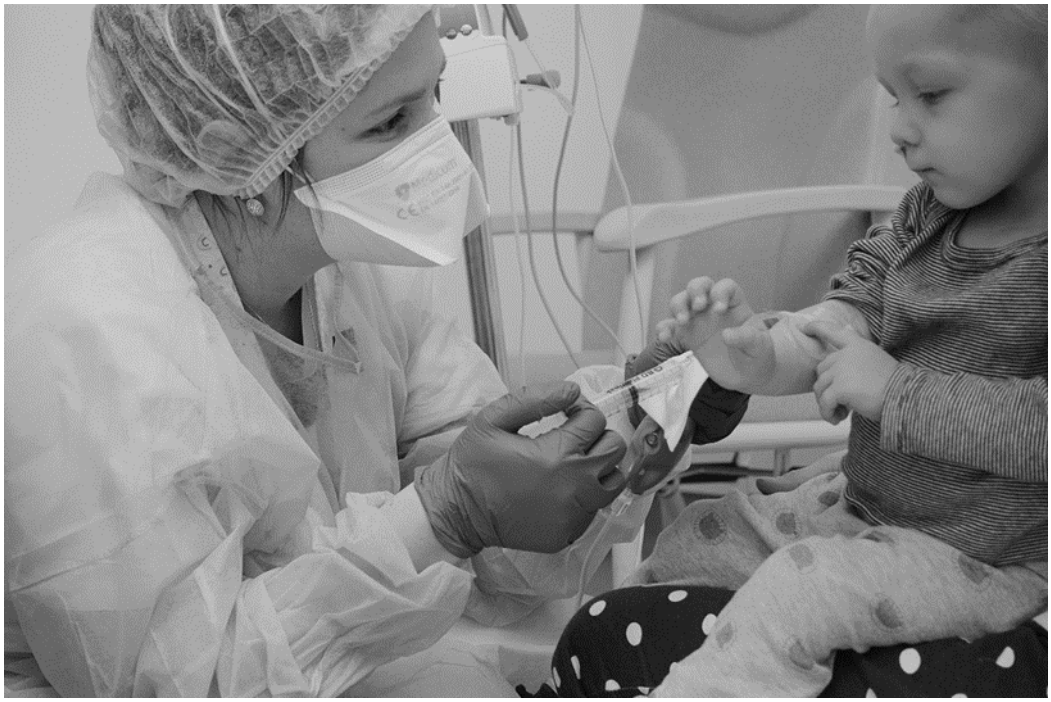
# CALENDAR 2023

| DATE | MEETING | LOCATION | NOTES |
|---|---|---|---|
| 2023 | | | |
| May 8-12(Mon-Fri) | EpSSG Spring Meeting & Association Assembly | SIOP Europe 2023 4th Annual Meeting Valencia | Confirmed |
| November 30-December 1 (Thu-Fri) | EpSSG Winter Meeting & Association Assembly | Barcelona | Confirmed |

# CALENDAR 2024-2026

| 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 |
| 2025 | | | |
| May 12-16 (Mon-Fri) | EpSSG Spring Meeting & Association Assembly | SIOP Europe 2025 6th Annual Meeting Budapest | Confirmed |
| December 4-5(Thurs-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 | TBD |
| December 3-4(Thurs-Fri) | EpSSG Winter Meeting & Association Assembly | Padova | Confirmed |

# 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 FUTURE MEETINGS

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and with the great
collaboration of all
EpSSG Members