NCRI
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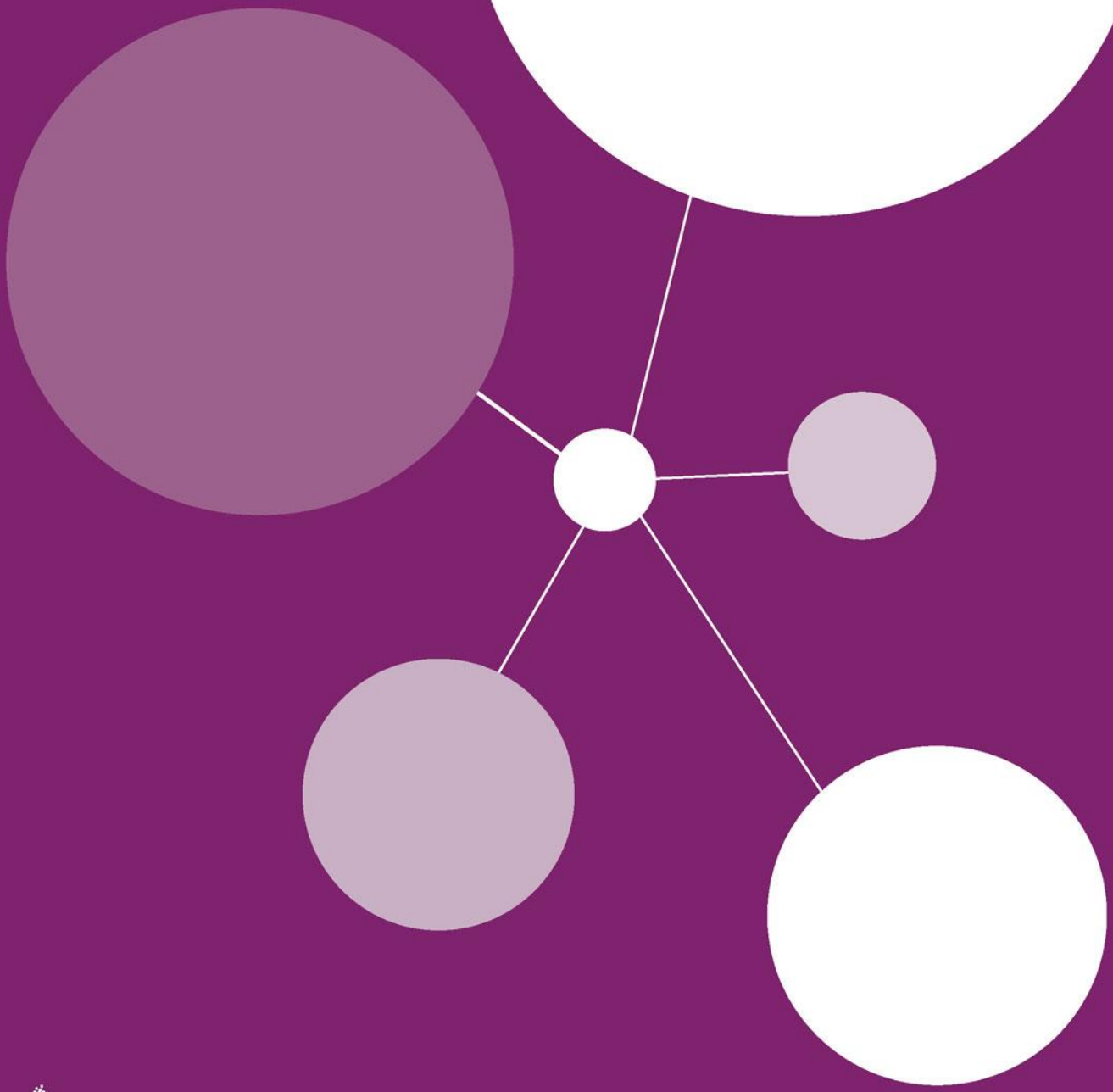
NCRI Sarcoma Clinical Studies Group

Annual Report 2015-16



Partners in cancer research

NCRI Sarcoma CSG Annual Report 2015-16

1. Executive Summary (including top 3 achievements in the year)

1. Preparation and planning of the Sarcoma CSG strategy day
    - The Sarcoma CSG have plans for a productive strategy meeting in May 2016 where we aim to identify areas of unmet need. We expect discussions for new trial development to sensor around:
        - Bone sarcoma
        - Metastatic sarcoma
        - Patient follow up and quality of life
    - Representatives from the NCRI Consumer Forum, Supportive & Palliative Care CSG, Psychosocial Oncology & Survivorship CSG, Teenage & Young Adults CSG, National Cancer Registration and Analysis Service (NCRAS), Sarcoma charities and TRACERx study to foster ideas of cross cutting research proposals.
2. First Publications for NRSTS 2005 study in major oncology journals
    - Conservative strategy in infantile fibrosarcoma is possible: The European paediatric Soft tissue sarcoma Study Group experience. Orbach, Daniel: Brennan, Bernadette: De Paoli, Angela et al; Eur J Cancer 2016:57; 1-9.
    - Outcome of extracranial malignant rhabdoid tumours in children registered in the European Paediatric Soft Tissue Sarcoma Study Group Non-Rhabdomyosarcoma Soft Tissue Sarcoma 2005 Study-EpSSG NRSTS 2005. Brennan B, De Salvo GL, Orbach D, De Paoli A, Kelsey A, Mudry P, Francotte N, Van Noesel M, Bisogno G, Casanova M, Ferrari A. Eur J Cancer. 2016;60:69-82.
3. Successful transition from the Chair of Professor Penella Woll to myself, with the Group understanding and taking forward the new strategic direction of NCRI moving from portfolio delivery to new portfolio trial design and set up, with the goal of recruiting all sarcoma patients to a portfolio trial.

2. Structure of the Group

After many years as a member (and previous Chair) of the Group, Professor Penella Woll rotated off the CSG. The Group acknowledged Professor Woll's massive contribution to sarcoma research in terms of Chair of the CSG and as a trialist. Mr Robert Wensley (consumer representative), Professor Bass Hassan (medical oncology), Dr Kevin Bradley (radiologist), Dr Jane Margetts (trainee representative) and Mr Jonathan Stevenson (trainee representative) also completed their terms on the CSG.

The Group welcomed Miss Ray Davis, Dr Sarah Pratap, Dr Rajesh Botchu, Mrs Sharon Forsyth and Professor Lee Jeys (Chair) who joined the CSG bringing expertise in consumer experience, medical oncology, radiology, trial co-ordination and sarcoma surgery respectively.

Following the call for trainee members, applications were received from four doctors in specialty training. Dr Alexander Lee (trainee in medical oncology, completing a PhD on the immunological aspects of sarcomas at the Institute of Cancer Research) and Dr Laura Forker (trainee in clinical oncology and PhD clinical fellowship in soft tissue sarcoma molecular biology funded by Cancer Research UK) were recently appointed as trainee representatives and will add vital experience in basic science research.

At the time of writing the report, the CSG has recently advertised for new members and depending on applications, expertise in basic science sarcoma research, sarcoma specialist nursing and psychosocial aspects of sarcoma care would help the Group fulfil its strategic direction.

The structure of the two Subgroups remains unchanged from previous years.

3. CSG & Subgroup strategies

Main CSG

The change of strategic direction of the NCRI towards trial development and initiation, rather than trail delivery, coupled with the needs to co-ordinate with the NIHR Clinical Research Network sarcoma clinical leads are the main focus of the strategy of the CSG. The Group is committed to developing studies, which can allow every patient with sarcoma in the UK to be enrolled. The lack of major studies into primary osteosarcoma or chondrosarcoma are recognised as major gaps in the current portfolio and these are research priorities for the Group.

The CSG plans to hold a strategy day on 5 May 2016. This will include discussions about areas of unmet need in sarcoma research in the UK, presentations from the Consumer Forum Chair, Supportive & Palliative Care CSG Chair, CSG statistical lead, Psychosocial Oncology & Survivorship CSG representative, surgical studies lead and several large studies (TRACERx, EUROEWINGS). After scene setting, the CSG will split into groups to brainstorm and propose studies to the Group. *POST MEETING NOTE* - the four study proposals that were generated were:

1. Osteosarcoma:
    - Recruit all new osteosarcoma patients within UK
    - Molecular biomarkers which predict outcome
    - Validation of novel classification of surgical margins
    - Imaging predictors of response to therapy pre-operatively (PET-CT, fMRI)
    - Randomisation of induction chemotherapy MiniMap vs AB
    - QOL outcomes for patients following surgical treatment including pain and functional assessment
2. Chondrosarcoma:
    - ‘What is the optimal surgical treatment of chondrosarcoma?’
    - Recruit all patients with benign and malignant cartilage tumours in UK.
    - Biobank of cartilage tumours for future research.
    - Investigation of molecular biomarkers, e.g. IDH 1 /2 mutation ratio.
    - Radiological studies of aggressive behaviour, e.g. fMRI.
    - Randomisation local control options for low grade tumours.
    - Ability to include new drugs from on-going Phase I/II studies.

3. Advanced Disease:
    - 'Can we improve the quality of life for patients with advanced sarcoma?'
    - Recruit all patients in UK with first presentation of locally recurrent or metastatic disease.
    - Supportive care studies with QoL outcomes.
    - Transitional studies with molecular biomarkers.
    - Randomisation of local control therapy (Surgery/RFA/Radiotherapy).
    - Cross cutting with other CSGs, especially the Psychosocial Oncology & Survivorship and Supportive & Palliative Care CSGs.
4. Post treatment surveillance:
    - 'Can we risk stratify follow up for sarcoma and personalise surveillance strategies?'
    - Recruit all patients with new sarcomas in UK.
    - Molecular & genetic biomarkers of outcome for sarcoma types.
    - PPI involvement of preferences to follow up.
    - Rationalisation of imaging efficacy in detection of advanced disease.
    - Cost benefit analysis of follow up methods.
    - Novel methods of follow up strategies (distance, nurse led).
    - QoL outcomes for cancer survivors.

At the end of the day, CSG leads were identified for each study and proposals are being developed to be presented to the CSG Group at the next meeting.

Bone Tumour Subgroup (Chair, Mr Craig Gerrand)

The Bone Tumour Subgroup has continued with an expanded membership in 2015/16, thanks to ongoing support from Bone Cancer Research Trust (BCRT).

- Ewing Sarcoma:
    - Recruitment to Euro-Ewing 2012 has continued in six European countries, with 147/600 patients randomised in the R1 arm, and 38/350 in the R2 arm. This represents excellent progress although a little behind target. The trial is now open in 24 NHS Trusts and 52 International sites and demonstrates the continuing commitment of the sarcoma community to clinical trials.
    - The translational/biological elements of this study are proceeding well - the allied pharmacokinetic study (PK2013 01) is recruiting to target (45/120 patients recruited, 16 centres open) as is the allied biological study (PI Birchill)
    - The rEECur study for relapsed Ewing sarcoma (PI McCabe), is a novel multiarm design with four treatment options; 48/275 patients have been randomised (25 in the UK) with opening in other European countries underway.
    - The LINES phase II study for relapsed Ewing sarcoma has been slower to recruit (n=16) and is awaiting review by the Data and Safety Monitoring Committee as funding is due to run out in November.
- Osteosarcoma:
    - There remains a lack of a first line drug study in osteosarcoma. A review of open studies in osteosarcoma in Europe and elsewhere by Dr Strauss and supplemented by Dr Pantziarka in May 2016 did not identify a study suitable for adoption. There are a number of Phase II studies open and a mechanism for sharing information about these studies is being explored.

- The UK-MEMOS trial (PI Hasan) is open and recruiting but there are key issues with recruitment, which appear related to the logistics of travel to the active UK sites.
- The prospective observational study "Optimisation of Circulating Tumour Cell Detection in Bone Sarcoma" is recruiting from five centres, with 13 of 30 recruited to date.

Young Onset Soft-tissue Sarcoma (YOSS) Subgroup (Chair, Dr Bernadette Brennan)

For rhabdomyosarcoma (RMS), the RMS 20015 study remains open, but FaR-RMS: A multiarm-multistage study for children and adults with localised and metastatic Frontline and Relapsed RhabdoMyoSarcoma new study proposal has been submitted for funding to CRC, and has been invited to the next stage for a full proposal to be submitted. It includes a phase I-III design to bring in both new chemotherapy combinations and mTOR inhibitor temsirolimus. It will also address questions on radiotherapy, PET assessment of response using a new stratification based on the genetic fusion status of the tumours. In relapsed RMS, the VIT study has reopened but a similar successor study proposal has been developed for this patient group, incorporating the addition of an mTOR inhibitor in a MAMS design, as part of the FaR-RMS application.

In non-rhabdomyosarcoma soft tissue sarcomas (NRSTS), EpSSG NRSTS 2005 remains open but the malignant rhabdoid stratum has been analysed and published. This has led to a meeting of a new European consortium for a European Rhabdoid study at all anatomical sites - EURO RHABDOID 2017. This study hopes to add a new agent, perhaps targeting the epigenetic pathway in rhabdoids alongside the established backbone from the EpSSG study now published. In addition, EUROJOSS study is moving forward with the aim of setting up the first all age trial in Europe for synovial sarcoma. It includes representation from all European sarcoma groups and the EpSSG which runs the largest paediatric sarcoma studies in Europe. Over-arching protocol includes low risk localised tumours, high risk localised tumours and metastatic. Randomised question at least and ancillary biology.

We also propose to convert the EpSSG NRSTS 2005 into a registry study allowing further collection of these extremely rare sarcomas in childhood. The stratum of infantile fibrosarcoma from NRSTS 2005 has also been published with similar plans for the Desmoid and the MPNST cohort. Membership has increased with two new TYA oncologists, Aisha Miah and Winette van der Graaf, responding to our challenges in the TYA population.

The Subgroup recognises the following continuing challenges:

- To increase participation of the TYA population in trials.
- The necessity for stable international consortia to develop trials where patient numbers in the UK are small.
- Obtaining access to new agents from pharma companies for younger patients.
- Funding the parallel biological studies in international trials

4. Task groups/Working parties

Gynaecological Sarcoma Working Party

This working party was set up in 2011 to develop trials and improve outcomes for this long-neglected patient group. The uterine leiomyosarcoma study (CI, Dr Hatcher) has been developed through the International Rare Cancers Initiative (IRCI) and opened last year. It evaluates adjuvant chemotherapy in completely resected high grade uterine leiomyosarcoma. The HGUS study (CI, Dr

Earl) has been developed by the same group and is now in set-up after obtaining CTAAC funding. It will be a randomized phase II study evaluating the role of maintenance cabozantinib in High Grade Uterine Sarcoma (HGUS) after stabilization or response to chemotherapy.

There are currently two Gynaecological Sarcoma EORTC studies are currently open in UK. Dr Helen Hatcher has stepped down from leading this group and Dr Charlotte Benson has taken over as Chair.

Lung Metastases Task Group

This task group is in development, led by Dr Aisha Miah. The group is working up a proposal for an observational study of all patients with lung metastases that will provide prospectively collected data on the outcomes of lung metastectomy, RFA, SABR, etc.

5. Patient recruitment summary for last 5 years

In the Sarcoma CSG portfolio, one trial has closed to recruitment and four opened. IMRiS (a phase II study of Intensity Modulated Radiotherapy in Sarcoma) was awarded funding from Cancer Research UK for a national study of Intensity Modulated Radiotherapy (IMRT) in Sarcoma. Dr Beatrice Seddon will be the lead investigator for the trial. The closure of major international trials, such EURAMOS recruitment to interventional studies has fallen. Newer trials are restricted to histologically or biologically defined patient subgroups, so accrual is less.

The strategy plans to address this by designing new studies that attempt to recruit large numbers of patients in sarcoma. The aim of the Group is to recruit as many patients with sarcoma in the UK to NCRI portfolio studies by designing studies that have a broader question, whether different patients can enter specific parts of the study, however, their outcome data can be used to get a broader understanding the biology of sarcomas and aid the development of future studies. This strategic aim should be possible given the limited number of centres that treat sarcoma in the UK, though funding for these studies is more problematic.

Table 1 Summary of patient recruitment by RCT/Non-RCT

Year	All subjects		Cancer patients only		% of cancer patients relative to incidence	
	Non-RCT	RCT	Non-RCT	RCT	Non-RCT	RCT
2011/2012	187	207	133	207	-	-

Table 2 Summary of patient recruitment by Interventional/Non-interventional

Year	All participants		Cancer patients only		% of cancer patients relative to incidence	
	Non-interventional	Interventional	Non-interventional	Interventional	Non-interventional	Interventional
2012/2013	194	272	151	272	4.7	7.8
2013/2014	43	195	25	195	-	-
2014/2015	145	115	145	115	-	-
2015/2016	58	130	58	130	-	-

6. Links to other CSGs, international groups and network subspecialty leads

Following the Chair's Forum and strategy day, the CSG has had cross fertilisation with the Consumer Forum, SPED Advisory Group, Psychosocial CSG, Supportive & Palliative Care CSG, Primary Care CSG and Teenage & Young adult CSGs. Several members of the CSG also sit on other CSGs and Dr Sandra Strauss is the subspecialty chair for NCRAS for sarcoma also sits on the CSG.

Links with the CRN subspecialty leads remains a difficulty, a joint meeting of the CSG and network leads had a disappointing turn out and the CSG is committed to fostering closer links, to ensure recruitment to available trials is at a maximum. Three regional leads for the network attended the strategy day and all were invited.

Dr Charlotte Benson continues to be involved with the EORTC and Dr Sandra Strauss provides a link with the USA Sarcoma Alliance for Research through Collaboration (SARC). Close collaborations are also maintained with EOI, SIOP and COSS through Professor Jeremy Whelan and Dr Bernadette Brennan. We are developing collaboration with the Scandinavian Sarcoma Group to open their GIST trial in the UK.

7. Funding applications in last year

Table 3 Funding submissions in the reporting year

Cancer Research UK Clinical Research Committee (CRUK CRC)			
Study	**Application type**	**CI**	**Outcome**
July 2015 (CTAAC)			
Three versus five years of adjuvant imatinib as treatment of patients with operable GIST with a high risk for recurrence: A randomised phase III study	Full application	Dr Venkata Bulusu	Funded
December 2015			
GeDDiS TransBio: Translational Study to investigate prognostic and predictive immune biomarkers in soft tissue sarcoma (STS)	Feasibility application	Dr Sandra Strauss	Not funded
May 2016			
MiRNA expression in plasma, tumour tissue and stem cells, a tool for measuring the effectiveness of chemotherapy in osteosarcoma	Full application	Professor Gordon Blunn	Not funded
FaR-RMS: A multiarm-multistage study for children and adults with localised and metastatic Frontline and Relapsed RhabdoMyoSarcoma	Outline application	Dr Meriel Jenney, Dr J Hans Merks, Dr Julia Chisholm & Professor Keith Wheatley	Full application invited

Four studies were submitted for CRUK CRC funding this year, one of which has been funded (three versus five years of adjuvant imatinib as treatment of patients with operable GIST with a high risk for recurrence: A randomised phase III study) and FaR-RMS has reached the last stage of funding application.

8. Collaborative partnership studies with industry

Six academic studies are partnerships with industry: MEMOS (Takeda), LINES (Astellas), Axi-STS (Pfizer), CASPS (AZ), PARAGON (AZ) and SCART (AZ). All six are open and recruiting. These trials address rare tumour types that would not otherwise have attracted the attention of pharma.

9. Impact of CSG activities

Our publications are testament to the high impact of our clinical research (Appendix 4). The routine management of bone and soft tissue sarcomas has been guided by NCRI supported trials. Ultimately our trials are practice-changing when they lead to new drugs being licensed (e.g. pazopanib for STS) or inform NICE, ESMO and ASCO practice guidelines. We anticipate that our NCRI-led trials, VORTEX and GeDDiS, will have such impact. The routine management of bone and soft tissue sarcomas has been guided by NCRI-supported trials. In particular, the EORTC trials 62931 and 62012 are the foundation of STS management in the UK and Europe. 62931 confirmed that adjuvant chemotherapy offers no survival advantage over observation alone in resected high-risk soft tissue sarcoma. 62012 demonstrated no survival advantage for doxorubicin and ifosfamide over doxorubicin alone in first line chemotherapy for advanced soft tissue sarcoma. Following analysis of the MMT95 and RMS 2005 trials, IVA remains the standard chemotherapy for rhabdomyosarcoma.

However, the recently published results of post-operative radiotherapy from EE99 study have showed marked reduction in the local recurrence of EWINGS, with a trend to improvement in overall survival, will change practice worldwide for this rare type of tumour. Forthcoming results from the EURAMOS study will answer the question about dose intensity in chemotherapy for osteosarcoma with presentations planned for late 2016. Publications from this Group this year have answered important questions about toxicity, gender differences and immunotherapy in osteosarcoma.

In paediatric sarcoma, trial results from EpSSG NRSTS 2005 protocol of intensive therapy showed this can be delivered to extracranial malignant rhabdoid patients with a possible improvement in outcome. Also that conservative therapy is possible in infantile fibrosarcoma as only three children required mutilating surgery and alkylating or anthracycline based chemotherapy was avoided in 71.0% of patients needing chemotherapy. These results will improve the life of children with sarcoma worldwide. The CSG has continued to engage with NICE appraising new drugs efficacy and NIHR funders on sarcoma related projects.

10. Consumer involvement

The CSG was glad to welcome Miss Ray Davis to the Group who brings a wealth of knowledge about Department of Health policy. Miss Davis and Mr Michael Maguire form an integral part of the CSG and were involved in the strategy day, together with Mr Richard Stephens (Consumer Forum Chair) and Mr Roger Wilson CBE (Sarcoma UK, elected Member of Cancer Research UK in 2015). Their combined knowledge and enthusiasm has helped to shape the research themes from the strategy day to put PPI at the heart of our research proposals, especially with the follow-up and advanced disease studies.

Michael Maguire and Ray Davis are developing a CRUK proposal about patients needs, where there are problems joining up all areas of patient needs and accessing useful information. They are considering developing an app for mobile phones to make access of information easier to aid recruitment and are liaising with the TYA CSG.

11. Open meetings/annual trials days/strategy days

The Group will hold a strategy day on 5 May 2016 at the Sarcoma UK offices in London. A networking evening meal will be spent generating areas of unmet research needs. The following

morning, scene setting will take place with talks from several members of other CSGs regarding cross-cutting research that may be possible. Short lectures from senior researchers on the CSG who have designed, launched and closed large studies is hoped to give the Group insight into the pitfalls in starting studies and their experiences. Statistical advice about novel trial design will be given by statistical lead Dr Piers Gaunt. Key sarcoma charities (Sarcoma UK and Bone Cancer Research Trust) together with Mr Richard Stephens will provide input about the consumer perspective to national research projects in Sarcoma, which was invaluable. The attendees will then brainstorm and develop four trial ideas. Following the meeting, CSG leads will be assigned to form trial proposals to be presented at the next CSG meeting in December 2016.

12. Priorities and challenges for the forthcoming year

Priorities:

1. To develop trial proposals from ideas developed in the strategy day. The lack of large studies in primary bone cancers of osteosarcoma & chondrosarcoma remain a focus for the CSG. The absence of a new first line agent should not deter the CSG in designing trials to answer the many questions that still remain for these diseases. Translational, biomarker, patient QOL, surgical intervention and drug regime questions remain which require answers. The intention from both study proposals in each disease is to attempt recruit all newly diagnosed patients on to a trial.

   The two other trial proposals are designed to investigate other areas of advanced disease and stratification of patient follow up. These trials are new areas of research, which are very patient focused and different to traditional drug intervention trials on the portfolio. They represent novel studies that will combine translational studies with patient outcomes from sarcoma.
2. To attempt to recruit a much higher percentage of sarcoma patients to trials in the UK. Currently the portfolio has several small studies and since the closure of large international studies in Osteosarcoma and Soft Tissue Sarcoma the number of sarcoma patients recruited to studies have fallen significantly. The design of studies should have broader questions, which allow umbrella style studies with innovative design, with more than one question to be answered and therefore data from every patient can be used for a greater understanding of sarcoma, tissue can be collected for biomarker or basic science research and useful patient related outcome measures (functional, psychosocial and oncological) can provide information for future projects.
3. To increase the relationships already fostered with other CSGs such as primary care CSG, supportive & palliative care CSG, psychosocial CSG, gynaecological CSG and teenage and young adult CSG, together with new relationships with SPED, biomarker and imaging advisory groups to bring new cross cutting project proposals with a more holistic approach to research into sarcoma.

Challenges:

1. To obtain national funding for innovative trial designs for the projects proposed from the strategy day. National funders have recently funded trials of innovative design and adding ‘value for money’ by answering several questions including biological questions may help applications be more successful, however, it remains a great challenge especially for a rare cancer type. The engagement of NCRI adopted charities, such as Sarcoma UK & Bone Cancer Research Trust, with the study proposals to help fund smaller scale feasibility

studies may help larger programme grants to be obtained. Statistical advice, CTU involvement and experience of senior researchers in the design of the feasibility studies and programme grant applications will be vital.

2. Recruitment to and management of existing portfolio studies will rely more heavily on CRN sub-speciality leads and their engagement to the studies will be important. This will also have major significance when launching new studies and the enthusiasm and co-operation of CSG members will be paramount in ensuring their success. Fortunately, with a limited number of treating centres for sarcoma, the membership and sarcoma community can levy influence on these centres.
3. Increasing recruitment to portfolio studies. To maintain NIHR funding for trial infrastructure, it will be important to maintain and increase recruitment. This is particularly difficult as trials become more niche in the era of precision medicine. It will be necessary to develop large observational studies with biomarker endpoints in order to balance the portfolio, otherwise recruitment will continue to fall.

13. Appendices

Appendix 1 - Membership of main CSG and subgroups

Appendix 2 – CSG and Subgroup strategies
- A – Main CSG Strategy
- B – Bone Tumour Subgroup Strategy
- C – Young Onset Soft-tissue Sarcoma (YOSS) Subgroup Strategy

Appendix 3 - Portfolio Maps

Appendix 4 - Publications in previous year

Appendix 5 - Major international presentations in previous year

Professor Lee Jeys (Sarcoma CSG Chair)

Appendix 1

Membership of the Sarcoma CSG

Name	Specialism	Location
Dr Ramesh Bulusu	Clinical Oncologist	Cambridge
Dr Aisha Miah	Clinical Oncologist	London
Dr Beatrice Seddon	Clinical Oncologist	London
Dr Paula Wilson	Clinical Oncologist	Bristol
Mr Michael Maguire	Consumer	Essex
Miss Ray Davis	Consumer	Bingley
Dr Malee Fernando	Histopathologist	Sheffield
Dr Charlotte Benson	Medical Oncologist	London
Dr Helen Hatcher	Medical Oncologist	Cambridge
Dr Sarah Pratap	Medical Oncologist	Oxford
Dr Sandra Strauss	Medical Oncologist	London
Professor Jeremy Whelan	Medical Oncologist	London
Dr Jane Margetts*	Medical Oncologist	Newcastle
Dr Bernadette Brennan	Paediatric Oncologist	Manchester
Dr Angela Edgar	Paediatric Oncologist	Edinburgh
Dr Rajesh Botchu	Radiologist	Birmingham
Mr Roger Wilson	Sarcoma UK	Shropshire
Mrs Sharon Forsyth	Senior Trials Coordinator	London
Dr Piers Gaunt	Statistician	Birmingham
Mr Craig Gerrand	Surgeon	Newcastle
Mr Jonathan Gregory	Surgeon	Manchester
Mr Jonathan Stevenson*	Surgeon	Shropshire
Professor Lee Jeys (Chair)	Surgeon	Birmingham

*denotes trainee member

Membership of the Subgroups

Bone Tumour Subgroup		
Name	**Specialism**	**Location**
Professor Susan Burchill	Cancer Biologist	Leeds
Dr Fiona Cowie	Clinical Oncologist	Glasgow
Mrs Kellie Vernon	Consumer	Birmingham
Dr Sandra Strauss	Medical Oncologist	London
Professor Jeremy Whelan	Medical Oncologist	London
Professor Donald Salter	Pathologist	Edinburgh
Dr Bernadette Brennan	Paediatric Oncologist	Manchester
Professor Susan Burchill	Paediatric Oncologist	Leeds
Dr Bruce Morland	Paediatric Oncologist	Birmingham
Mr Matthew Sydes	Statistician	London
Professor Keith Wheatley	Statistician	Birmingham
Mr Craig Gerrand (Chair)	Surgeon	Newcastle
Professor Robert Grimer	Surgeon	Birmingham
Mr Jonathan Stevenson*	Surgeon	Shropshire

Young Onset Soft tissue Sarcoma (YOSS) Subgroup		
Name	**Specialism**	**Location**
Dr Henry Mandeville	Clinical Oncologist	Sutton
Dr Anna Kelsey	Histopathologist	Manchester
Dr Helen Hatcher	Medical Oncologist	Cambridge
Dr Palma Dileo	Medical Oncologist	London
Dr Madeleine Adams*	Paediatric Oncologist	Cardiff
Dr Bernadette Brennan (Chair)	Paediatric Oncologist	Manchester
Dr Julia Chisholm	Paediatric Oncologist	London
Dr Meriel Jenney	Paediatric Oncologist	Cardiff
Dr Kieran McHugh	Radiologist	London
Mr Tim Rogers	Surgeon	Bristol
Dr Janet Shipley	Translational Scientist	London

*denotes trainee member

Appendix 2

CSG & Subgroup Strategies

A – Main CSG Strategy

Sarcoma CSG Strategy: May 2016 – May 2018

This strategy timeline has been produced to define the Sarcoma Research Strategy Plan and its implementation and will be reviewed and updated at each CSG meeting (NB supported by All)
The document is composed of the following:

Page 2 – 6: NCRI Sarcoma CSG Strategy: plan of implementation, containing agreed strategic objectives (1-6), specific actions, CSG leads and proposed deadlines.

Sarcoma CSG Members		Responsibility
LJ	Lee Jeys	CSG chair
BB	Bernadette Brennan	Young Onset Soft Tissue Sarcoma Subgroup Chair
CG	Craig Gerrand	Bone Sarcoma Subgroup Chair
RB	Ramesh Bulusu	Clinical Oncology
AM	Aisha Miah	Clinical Oncology
BS	Beatrice Seddon	Clinical Oncology
PW	Paula Wilson	Clinical Oncology
MM	Michael Maguire	Consumer representative
RD	Ray Davis	Consumer representative
MF	Malee Fernando	Histopathology
CB	Charlotte Benson	Medical Oncology
HH	Helen Hatcher	Medical Oncology
SP	Sarah Pratap	Medical Oncology
SS	Sandra Strauss	Medical Oncology / NCRAS Chair
JW	Jeremy Whelan	Medical Oncology
JM	Jane Margetts	Medical Oncology
AE	Angela Edgar	Paediatric Oncology / TYA Chair
RBo	Rajesh Botchu	Radiology
RW	Roger Wilson	Sarcoma Charity / Comsumer Representative
SF	Sharon Fortsyth	Trial Co-ordinator
PG	Piers Gaunt	Statistical Lead
JG	Jonathan Gregory	Surgery / SPED CSG
JS	Jonathan Stevenson	Surgery
MW	Mary Wells	Psychosocial CSG
SA	Sam Ahmedzai	Supportive and Palliative Care CSG Chair
DH	Dominque Heymann	Sarcoma Basic Scientist
UV	Ulla Ventham	PA
NK	Nicola Keat	NCRI Exec

Strategic objective	Action	CSG Lead	Date	Outcomes
1a. Portfolio development (general)	Establish a set of priorities for the development and set up of studies that takes account of the NIHR portfolio, international agenda, available funding opportunities and clinical need	ALL	Document key priorities at Strategy Day 5th May 2016 Review Dec 2016	Review Portfolio priorities 6-monthly at CSG meetings
1b. Portfolio development – Advanced disease	Develop a new portfolio study of advanced disease. New study proposed to include all patients with bone and soft tissue sarcoma with a new presentation of metastatic disease. Aim of study is to investigate current treatment with goal to improve quality of life for advanced disease in a longitudinal cohort study with randomisation of local control options, utilising innovative study design . Study to include :- • Supportive care studies with QOL outcomes • Transitional studies with molecular biomarkers • Local control randomisation • Interaction with CRN subspecialty leads • Cross cutting with other CSGs	AM, JW, SS, SA	Identified at Strategy Day 5th May 2016 Progress review 6 monthly at CSG meetings	Working group to develop study / initial feasibility study/ application for programme grant/ leads to fill gaps in portfolio/ leads to engage with other CSGs.
1c. Portfolio development Osteosarcoma	Develop a new portfolio study of osteosarcoma following the hiatus left by a lack of follow up study to EURAMOS. The lack of a new drug has hampered a follow up study, however, many questions remain. Aim of study is recruit all new patients with osteosarcoma in UK. Study to include :- • Molecular biomarkers which predict outcome • Validation of novel classification of surgical margins • Imaging predictors of response to therapy pre-operatively • Randomisation of induction chemotherapy MiniMap vs AB • Interaction with CRN subspecialty leads • Cross cutting with other CSGs • QOL outcomes for patients	BB, SS, AE, SP, RBo, LJ, PG	Identified at Strategy Day 5th May 2016 Progress review 6 monthly at CSG meetings	Working group to develop study / initial feasibility study/ application for programme grant/ leads to fill gaps in portfolio/ leads to engage with other CSGs.
1d. Portfolio development Chondrosarcoma	Develop a new portfolio study of chondrosarcoma. Chondrosarcoma is now most common primary bone sarcoma in UK and has no studies on the portfolio. Aim of study is to recruit all patients presenting to bone sarcoma treating centres with benign or malignant cartilage tumours into longitudinal cohort study with randomisation of local control options for low grade cartilage tumours. Study to include :- • Biobank of cartilage tumours for future research • Investigation of molecular biomarkers (IDH 1 /2 mutation ratio) • Radiological studies of aggressive behaviour (fMRI) • Randomisation local control options for low grade tumours • Ability to include new drugs from on-going Phase 1/11 studies	LJ, JG, JS, CG, Rbo, PG, DH	Identified at Strategy Day 5th May 2016 Progress review 6 monthly at CSG meetings	Working group to develop study from 5 primary bone centres / initial feasibility study with bone sarcoma charity/ application for programme grant/ leads to fill gaps in portfolio/ leads to engage with other CSGs.

Strategic objective	Action	CSG Lead	Date	Outcomes
1e. Portfolio development – Follow up	Develop a new portfolio study to identify optimal methods of follow up of sarcoma patients following treatment, leading to risk stratification and personalised treatment plans. Current methods of post treatment surveillance is variable. Given the large geographic distances travelled to follow up clinics, novel methods of follow up may have benefit. Currently all types of sarcoma are followed up in a similar schedule, risk stratification may allow personalised regimes. Aim of study would be to recruit all new patients with sarcoma in UK to a follow up study. Study to include:- • Molecular & genetic biomarkers of outcome for sarcoma types • PPI involvement of preferences to follow up • Rationalisation of Imaging efficacy in detection of advanced disease • Cost benefit analysis of follow up methods • Novel methods of follow up strategies (distance, nurse led) • QOL outcomes for cancer survivors	JG, BS, CG, MW, RW, RD, MM, PG, FM,	Identified at Strategy Day Day 5th May 2016 Progress review 6 monthly at CSG meetings	Working group to develop study / initial feasibility study/ application for programme grant/ leads to fill gaps in portfolio/ leads to engage with other CSGs.
1f. Portfolio development – Surgical wounds	Continue to develop a surgical study (Whispar) which is a randomised trial of surgical dressings for soft tissue sarcoma wounds. The study randomises between traditional occlusive dressings and topical negative pressure dressings. Initial pilot study has been undertaken winning a prize at the British Sarcoma Group meeting 2016. Aims to recruit patients undergoing surgery for soft tissue sarcomas at units across UK.	JG & WHISPaR study group	Identified at surgical studies meeting 2014 Progress review 6 monthly at CSG meetings	Working group to apply for an RfPB or HTA grant / leads to fill gaps in portfolio
1g. Interaction with international research groups	Identify leads within the CSG to link with the following research groups: EORTC COG euroSARC Conticanet	LJ	May 2016	To keep under review at 6 monthly CSG meeting
1h. Interaction with Cross Cutting groups	Identify leads within the CSG to link with the following cross cutting CSGs and advisory groups: •Primary Care CSG •Biomarker Advisory group •Screening, Prevention and Early Diagnosis (SPED) Advisory Group •CTRAD •Supportive and Palliative Care CSG	LJ	May 2016	To keep under review at 6 monthly CSG meeting

Strategic objective	Action	CSG Lead	Date	Outcomes
1i. National Cancer Registration and Analysis Service (NCRAS)	Establish clear link with Sarcoma Clinical Reference Group Maintain clear links with NCIN the use of data to inform study design and take over long term follow-up	SS / ALL	Report 6 monthly at CSG meeting	NCRAS to have standing item on 6 monthly CSG meetings
2. Key research priority areas	**Surgery** • Increase number of surgical trials within portfolio • Set up a surgical studies subgroup to stimulate research ideas • Local control for chondrosarcoma • Prospective evaluation of surgical margins for osteosarcoma **Osteosarcoma / Chondrosarcoma:** • Establish further trials for these tumour types **Advanced disease :** • Establish further studies for metastatic disease **QOL / Follow up:** • Embed QOL questions into all sarcoma studies • Establish further studies for post treatment surveillance • Embed supportive care studies into future protocols **Translational:** •Work with key clinical and scientific groups to develop embed translational questions into all studies and build translational research platform	LJ JG LJ BB/LJ BB/LJ AM MW JG SA All	May 2016 May 2016 May 2016 May 2016 On-going	Outline proposals to CSG DEC 16 update on progress 6 monthly CSG meeting s
3a. Raising awareness and profile	Regular dissemination of study recruitment activity and outcomes through newsletters, annual meetings and Annual Report and submission of meeting abstracts Communications about new studies with CRN subspecialty leads Engage with sarcoma charities to promote NCRI work during Sarcoma awareness week Have regular NCRI sessions at sarcoma national meetings (BSG, BOOS)	LJ/All UV/All RW/All LJ/All	On-going 2016 2016 On-going	LJ to feedback Participate in future NCRI Subspecialty leads / CSG meetings Discuss next CSG meeting Dec 2016

Strategic objective	Action	CSG Lead	Date	Outcomes
3b. Ensuring successful delivery of studies through integration with NIHR CRN: Cancer	• CSG members to commit to delivering studies developed by the CSG • Interaction with LCRN Subspecialty Leads to determine placement of new studies and address barriers to actively recruiting patients • Monitor recruitment to portfolio studies, esp those developed by the CSG to ensure delivery to time and target • Contribute as far as possible to NIHR CRN: Cancer Speciality Objectives so they reflect what LCRNs need to deliver to ensure lung cancer patients can access the full portfolio of studies within UK	ALL ALL ALL ALL	On-going On-going On-going On-going	Recruit CSG-led studies to time and target Good regional placement of studies Meet NIHR CRN Speciality Objectives
3c. Maximise output from clinical trials	• Establish working groups for new studies within 6 weeks of funding award to facilitate swift set up, including representation from CI, CRCTU, NIHR CRN: Cancer • Ensure Translational, QOL & supportive questions embedded into all studies opened • Design studies which aim to recruit as many sarcoma patients as possible by asking multiple questions within same study	CI/CTUs All All	On-going	Update at six monthly CSG meetings
4. Strengthen UK wide and international working	Refine prioritisation process for international clinical trials to be submitted for funding to optimise the timing and success of applications Identify UK selling points for sarcoma research to identify and promote the flagships studies on the portfolio Work to badge academically sponsored NCRI CSG studies as 'NCRI study into x' Work to ensure research remains core to NHS service and is recognised in all job plans .	All All All	On-going On-going May 2016 May 2016	Update at six monthly CSG meetings

Strategic objective	Action	CSG Lead	Date	Outcomes
5. CSG structure and function	Establish Surgical Studies subgroup	JG/CG/LJ	May 2016	Establish appropriate representation at CSG meetings to foster research ideas and new studies Diversify portfolio studies to include areas of unmet need
	Working Party for new study proposals from strategy day	LJ/JG/BB/AM	May 2016	
	Diversify membership of CSG to include Basic scientist, Psychosocial, Specialist nursing experience in membership to reflect need for portfolio studies in these areas.	LJ/NK	May 2016	
	Regular invitation to attend CSG from other relevant CSGs, NCRAS and Advisory Groups depending on agenda items & proposals	LJ/NK/UV	May 2016	
	Identify mentors for future trainee registrars in the CSG / subgroups	LJ	May 2016	
	Identify mentors for new PPI members in CSG / subgroups	LJ	May 2016	
6. Patient and Public Involvement and Impact	Ensure consumers remain associated with the development of every new study at an early stage	All	On-going	Ensure studies have relevance to consumers through CSG meeting / reports
	Consider developing research studies to address key questions of concern to PPI representatives and other consumers	MM/RD to bring questions to the group	On-going	

B – Bone Tumour Subgroup Strategy

The strategy of the Bone Tumour Subgroup is outlined and in keeping with strategy of the main CSG to develop new studies for Osteosarcoma and Chondrosarcoma, taking forward study ideas from the strategy day on 5 May 2016 to funding application and implementation.

C – Young Onset Soft-tissue Sarcoma (YOSS) Subgroup Strategy

Agreed strategic priorities for YOSS:

1. To open a first line study in Rhabdomyosarcoma across all ages.
2. To build on current relapse studies in RMS using VIT as backbone.
3. To develop an all age European study in Synovial Sarcoma.
4. To build on the outcomes of other rare sarcomas from the NRSTS study to develop further clinical trials specifically Rhabdoid tumours at all sites.
5. To embed biological studies, biomarkers and novel targets into clinical trial portfolio.

1. and 2. FaR-RMS: A multiarm-multistage study for children and adults with localised and metastatic Frontline and Relapsed RhabdoMyoSarcoma new study proposal has been submitted for funding to CRC, and has been invited to the next stage for a full proposal to be submitted.

In summary, the specific proposal includes a comprehensive clinical research programme will evaluate several therapies addressing survival and long term morbidity in children, teenagers and adults with RMS. Patients with newly diagnosed and relapsed RMS will enter separate study arms (A and B).

3. To develop an all age European study in Synovial Sarcoma

The first meeting of EUROJOSS in order to set up the first all age trial in Europe for synovial sarcoma included representation from all European sarcoma groups and the EpSSG which runs the largest paediatric sarcoma studies in Europe-Italians, French sarcoma group, Scandinavian Sarcoma Group, UK, Germany, Poland and the Netherlands. Agreements - need for a co-operative perspective study at a European level, multi-national, multi-institutional joint study for adult and paediatric patients. Over-arching protocol including low risk localised tumours, high risk localised tumours and metastatic. Randomised question at least and ancillary biology. A randomised study may conclude a MAMS design re considering backbone therapy for high risk synovial sarcoma +/- targeted agents. Arms include high dose single agent ifosfamide, trabectadin, ifosfamide/dox, +/- pazopanib.

Currently work is looking at collecting more samples to examine the role of genomic index (GI). Trying to define better high risk localised tumour group +/- metastatic patients in terms of planning a MAMS design hence discussion with biostatistician in the Bordeaux Unit.

4. To build on the outcomes of other rare sarcomas from the NRSTS study to develop further clinical trials

The meeting of a new European consortium for a European Rhabdoid study at all anatomical sites - EURO RHABDOID 2017. This study hopes to add a new agent perhaps targeting the epigenetic pathway in rhabdoids alongside the established backbone from the EpSSG study now published.

5. To embed biological studies, biomarkers and novel targets into clinical trial portfolio

An application to Horizon 2020 with an overall aim of this biological proposal to increase the rate of survival and improve the quality of life for children with STS, by optimising the effectiveness of established treatment protocols and promotion of basic research by specifically prospectively test

novel molecular markers for risk stratification of patients, assess the efficacy of circulating biomarkers for Minimal Residual Disease (MRD) and identify rationale and provide pre-clinical evidence for new molecular therapeutic targets/specific anti-cancer drugs alongside conventional treatments. Lastly to incorporate and assess the best pre-clinically tested compounds into treatment protocols. This was unfortunately unsuccessful but alongside applications for new trials in STS further applications are been made to under pin these with biological sample collection and studies.

Appendix 3

Portfolio maps

NCRI portfolio maps

Sarcoma

Map B – Bone
Click ↓ below to reset map

		1st line advanced	2nd line advanced	Observational / translational	Primary treatment
All bone sarcoma	All	FPA008		CREATE ISKS study Optimisation of CTCs	IMRiS
Chondrosarcoma	All				
Ewing's	All	Euro Ewing 2012 rEECur	LINES	Genotype and ph	Euro Ewing 2012 Pharmacokinetic rEECur PREDICT
Osteosarcoma	All		MEMOS		

Filters Used:
Active Status: All, **CSG Involvement**: All, **Funding Type**: All, **Phase**: All

In Set-Up Pending .. Open Single CSG
Open Multi CSG

Appendix 4

Publications in the reporting year

EURAMOS-1

Whelan JS, Bielack SS, Marina N, Smeland S, Jovic G, Hook JM, et al. EURAMOS-1, an international randomised study for osteosarcoma: results from pre-randomisation treatment. Ann Oncol. 2015;26(2):407-14

Bielack SS, Smeland S, Whelan JS, Marina N, Jovic G, Hook JM, et al. Methotrexate, Doxorubicin, and Cisplatin (MAP) Plus Maintenance Pegylated Interferon Alfa-2b Versus MAP Alone in Patients With Resectable High-Grade Osteosarcoma and Good Histologic Response to Preoperative MAP: First Results of the EURAMOS-1 Good Response Randomized Controlled Trial. J Clin Oncol. 2015;33(20):2279-87

EpSSG NRSTS 2005

Bernadette Brennan, Gian Luca De Salvo, Daniel Orbach et al. Outcome of extracranial malignant rhabdoid tumours in children registered in the European paediatric Soft tissue Sarcoma study Group Non- Rhabdomyosarcoma Soft Tissue Sarcoma 2005 study
Eur J Cancer 2016 - *in press*

Conservative strategy in infantile fibrosarcoma is possible: The European paediatric Soft tissue sarcoma Study Group experience

Orbach D, Brennan B, De Paoli A et al. Eur J Cancer. 2016:57;1-9

EuroEWING 99

Foulon S, Brennan B, Gaspar N, Dirksen U, Jeys L et al Can postoperative radiotherapy be omitted in localisedstandard-risk Ewing sarcoma? An observational study of the Euro-E.W.I.N.G group. Eur J Cancer. 2016 Jul;61:128-36.

Bedetti B, Wiebe K, Ranft A, Aebert H, et al Local
control in Ewing sarcoma of the chest wall: results of the EURO-EWING 99 trial. Ann Surg Oncol. 2015 Sep;22(9):2853-9.

van den Berg H, Paulussen M, Le Teuff G, Judson I et al Euro-EWING99 Group. Impact of gender on efficacy and acute toxicity of alkylating agent -based chemotherapy in Ewing sarcoma: secondary analysis of the Euro-Ewing99-R1 trial. Eur J Cancer. 2015 Nov;51(16):2453-64.

Appendix 5

Major international presentations in the reporting year

SCART trial

Young R, Poyser C, Crack L, Dockrell D, Bowman C, Billlingham L, Bower M, Westwell S, Leahy M, Woll P. A UK national phase I/II clinical trial of a MEK1/2 inhibitor combined with highly active anti-retroviral therapy for HIV-associated Kaposi's sarcoma. Eur J Cancer. 2015. 51:S699. Presentation at ESMO 2015

GeDDiS trial

Beatrice Seddon, Jeremy Whelan, Michael Leahy, Penella Woll, Fiona Cowie, Christian Rothermundt, Zoe Wood, Sharon Forsyth, Paul Patterson, Stephen Nash, Sandy Beare. GeDDiS: A prospective randomised controlled phase III trial of gemcitabine and docetaxel compared with doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft tissue sarcomas (EudraCT 2009-014907-29). American Society of Clinical Oncology Annual Meeting, Chicago, USA. Abstract 10500, June 2015.

Beatrice Seddon, Jeremy Whelan, Michael Leahy, Penella Woll, Fiona Cowie, Christian Rothermundt, Zoe Wood, Sharon Forsyth, Paul Patterson, Stephen Nash, Sandy Beare. GeDDiS: A prospective randomised controlled phase III trial of gemcitabine and docetaxel compared with doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft tissue sarcomas (EudraCT 2009-014907-29). Connective Tissue Oncology Society Annual Meeting, Salt Lake City, USA, November 2016.

Beatrice Seddon, Jeremy Whelan, Michael Leahy, Penella Woll, Fiona Cowie, Christian Rothermundt, Zoe Wood, Sharon Forsyth, Paul Patterson, Stephen Nash, Sandy Beare. GeDDiS: A prospective randomised controlled phase III trial of gemcitabine and docetaxel compared with doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft tissue sarcomas (EudraCT 2009-014907-29). British Sarcoma Group Annual Meeting, Manchester, UK, February 2016.