



**Randomised trial of Volume of post-operative
radiotherapy given to adult patients with eXtremity
soft tissue sarcoma**

Version 6
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Randomised trial of volume of post-operative radiotherapy given to adult patients with extremity soft tissue sarcoma

MAIN SPONSOR

*The University of Sheffield will act as the main sponsor,
and the University of Birmingham will be sub contracted to carry out the co-ordination of the study.*

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VORTEX:

Randomised trial of volume of post-operative radiotherapy given to adult patients with extremity soft tissue sarcoma

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any suggested changes to the protocol must be approved by the VORTEX Trial Team prior to seeking approval from the Independent Ethics Committee.

This study will be conducted under the auspices of the Cancer Research UK according to the current guidelines for Good Clinical Practice and in accordance with the World Medical Association (WMA) Declaration of Helsinki (1996).

Investigators Signature _____
Printed name _____
Name of Institution _____
Date _____

The Principal Investigator should sign and submit the original copy of this page to the VORTEX Study Office

Study summary

VORTEX: Randomised trial of volume of post-operative radiotherapy given to adult patients with extremity soft tissue sarcoma

Aims/Objectives: The aim of this trial is to assess if a reduced volume of post-operative radiotherapy increases limb function without compromising local control

Outcomes:

Primary: Limb functionality and time to local recurrence

Secondary: Soft tissue and bone toxicity, disease free-survival, overall survival time and overall level of disability

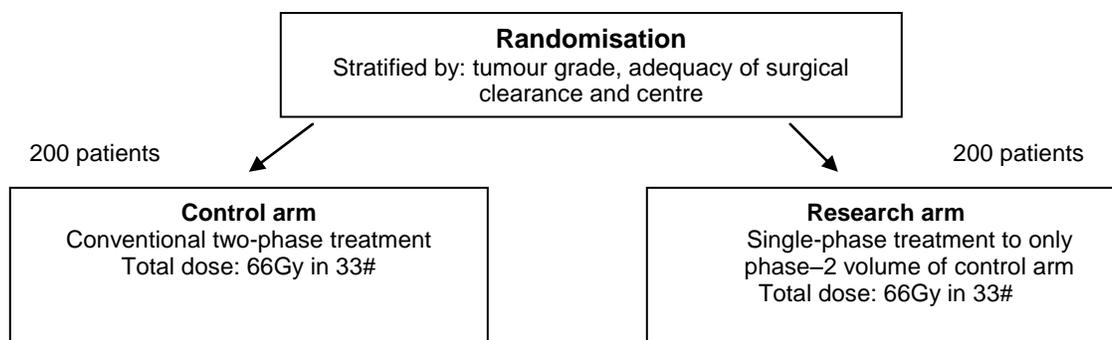
Main (but not exhaustive) inclusion criteria:

- Histologically proven soft tissue sarcoma. Imaging and pathology from first surgery are required
- Microscopically irradical surgical margin
- Lesion originates in extremity
- No prior radiotherapy to the local site
- Protocol treatment is to begin within 12 weeks of surgery
- Patients must be 16 years of age or older
- Male and female of reproductive potential must use medically acceptable contraception during the duration of radiation treatment and for three months following the completion of the radiation treatment

Main (but not exhaustive) exclusion criteria:

- Local recurrence after previous treatment of sarcoma or more than 3 months after previous definitive surgery
- Surgery has left macroscopic tumour in situ
- Patient has regional nodal disease or unequivocal distant metastasis
- Use of neoadjuvant or adjuvant chemotherapy
- Prior or concurrent malignancy (except adequately treated non-melanomatous carcinoma of the skin or in situ carcinoma of the cervix) within the last 3 years.

Diagrammatic representation of treatment allocation (if applicable):



Investigations required prior to randomisation:

- Haematology: FBC with differential
- Radiology: chest X-ray, CT thorax and MRI local site
- Wound assessment
- Completion of the Toronto Extremity Salvage Score questionnaire
- Completion of the Patient Perceived Change of Status questionnaire

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1. INTRODUCTION

Background

Soft tissue sarcoma accounts for about 1 per cent of adult cancers with an incidence of 37 cases per million person years. Approximately 1200 cases are reported each year in the U.K. Almost half of all soft tissue sarcomas occur in the limbs. In most cases there is no clear aetiology. However, there are clear associations with genetically linked disorders, such as von Recklinghausen's neurofibromatosis, tuberous sclerosis, basal cell naevus and Li Fraumeni syndromes.

The indications for the use of radiotherapy in extremity soft tissue sarcomas were recently agreed at an international consensus meeting in Milan (Appendix 1). All high grade sarcomas, apart from those rare tumours which are superficial or <5cm in size and radically excised, are considered to benefit from the addition of radiotherapy. Randomised trials have demonstrated the effectiveness of radiotherapy in reducing local recurrence in both high and low-grade tumours (Yang *et al*; 1998). Where radiotherapy was given by brachytherapy this effect was not seen in low-grade tumours (Harrison *et al*; 1993). There is no evidence from these randomised trials that local control influences survival. However, quality of life and limb function are dependent on achieving a good local control and upon radiotherapy dose and technique (Nielsen *et al*; 1991; Peat *et al*; 1994).

Adjuvant Radiotherapy

The addition of high dose radiotherapy to soft part resection has permitted the practice of limb conservation in the management of limb and limb girdle soft tissue sarcomas in a number of centres (Abbatucci *et al*; 1984; Barkley *et al*; 1988; Brennan *et al*; 1985; Carabell and Goodman, 1981; Eilber *et al*; 1985; Lindberg *et al*; 1981). The local control rates achieved by this combination have been similar to that from amputation without prejudicing patient survival (Potter *et al*; 1986). The goal of combined treatment is a functioning limb without local recurrence. The effect of local recurrence on survival remains uncertain. Some authors associate local recurrence with decreased survival (Collin *et al*; 1988, Stotter *et al*; 1990).

The results of the Canadian SR-2 study, where patients were randomised to receive pre-operative or post-operative radiotherapy were interesting. Those treated with pre-operative radiotherapy received 50Gy in 25 fractions as opposed to 66Gy in 33 fractions for the post-operative group. The study was stopped after a planned interim analysis showed that there was a statistically significant increase in wound complication rate in the pre-operative arm. This increased complication rate was confined to those patients with tumours in the thigh. The completion of the study to planned size would not have resulted in a non-statistically significant result.

A correlation was observed with bone toxicity and the TESS score. Maximal radiation dose and Musculo Skeletal Tumour Rating Scale (MSTS) were associated with joint toxicity and field area was associated with oedema. Results from this study suggest that both field area and total dose are contributory factors to greater subcutaneous tissue toxicity and oedema and that both dose and field size are important in determining morbidity and function following a combination of surgery and radiotherapy in extremity sarcoma. This study also confirmed that the use of pre-operative radiotherapy in general results in use of smaller radiotherapy fields. A proportion of the patients in this trial did receive a post operative boost where the surgical margin was poor but on average the total dose received was also lower in the pre-operative radiotherapy arm. This has previously been demonstrated by (Nielsen *et al*; 1991) and (Robinson *et al*; 1991).

Long term follow-up of the functional consequences and morbidity of the two treatment arms has been reported. These were compared using the RTOG scores for toxicity to skin and subcutaneous tissue, bone, joint stiffness and oedema and by evaluating a relationship of these endpoints to function as measured by the Musculo Skeletal Tumour Rating Scale (MSTS) and the Toronto Extremity Salvage Score (TESS) 2 years post treatment. Significantly more patients in the post operative arm had grade 2 or greater subcutaneous fibrosis, more frequent oedema and joint stiffness. Field size was predictive of greater rates of fibrosis and joint stiffness and marginally predictive of oedema. Fibrosis, joint stiffness and oedema adversely affect patient function (Davis *et al*; 2004).

Surgical margins and radiotherapy dose

A survey of international practice in terms of surgical margins and dose has been carried out and indicated that approximately 60% of clinicians applied a 5cm margin to the surgical scar when planning post-operative radiotherapy and the same margin to the tumour bed when planning pre-operative treatment (Robinson 1998 personal communication). Lindberg and Suit have previously recommended larger margins (7-15cm) depending on size and grade of tumour. There are very few studies in the literature looking at the target volume used when planning radiotherapy and this tends to be poorly reported. One group found a remarkable difference in 5-year local control where the margin was <5cm (30%) or \geq 5cm (93%) (Mundt 1995). This conflicts with the brachytherapy data where acceptable results are achieved using 4cm margins longitudinally and 2cm laterally. (Fein *et al*; 1995). This author also reported that local control was dose dependent. Fein 1995 noted that patients receiving <62.5Gy had 5-year local control of 78% v 95% where the dose was >62.5Gy. (Robinson *et al*; 1992) failed to demonstrate a variation in local control according to dose, although the response rate to pre-operative radiotherapy was clearly dose dependent.

It is common practice for clinicians to use a 'shrinking field' technique for the treatment of extremity sarcomas. A typical phase 1 dose is 50Gy in 25 daily fractions followed by a 10-16Gy boost in 5-8 fractions. A recent publication from the Royal Marsden Hospital has suggested that as in other tumour sites the great majority of local recurrences occur within the high dose volume (Cleator, 2001). This rises the question regarding the large volume phase 1 being necessary or if the boost is necessary where an adequate surgical margin has been achieved.

There is currently an influx of new radiotherapy techniques such as Intensity-Modulated Radiotherapy (IMRT) being introduced, which will permit the selective sparing of normal tissues. There is a need to accurately determine the volumes that can safely be spared before implementing these techniques. Prior to considering the implementation of IMRT techniques (Millar, 2001) it is important to obtain relevant and accurate dose/volume data, which can be collated with functional outcomes.

Rationale

The timing of the radiotherapy in relation to surgery, the extent of surgery required, the extent of apparently normal tissue around the tumour bed to be included in the irradiated volume, and the best dose and fractionation schedule are still unresolved issues. There have been no systematic reviews or randomised trials in the field of extremity soft tissue sarcoma in adult patients. It is now time to obtain data from a prospective study of radiotherapy margins in the treatment of adult extremity soft tissue sarcoma. There is no evidence that the international practice of irradiating large volumes of normal tissue is necessary. The VORTEX study has been designed to address this question.

A positive result would change international practice and significantly reduce the morbidity of radiotherapy treatment in this group of patients.

2. OBJECTIVES

The objective of this trial is to assess if a reduced volume of post-operative radiotherapy increases limb function without compromising local control.

Outcome Measures

Primary outcome measures

- **Limb functionality:** as measured by the Toronto Extremity Salvage Score (TESS).
- **Time to local recurrence:** defined in whole days, as the time from randomisation into the trial to the occasion when a local recurrence is confirmed by biopsy. For those patients who are not observed to have a local recurrence during the course of the study, the time to local recurrence will be censored at the last follow-up date.

Secondary outcome measures

- **Soft tissue and bone toxicity:** measured by the RTOG scoring system.
- **Disease-free survival time:** defined in whole days as time from randomisation into the trial to either local or distant recurrence or death (whichever occurs first).
- **Overall survival time:** defined in whole days as time from randomisation into the trial to death.
- **Overall level of disability:** as measured using the two general questions on the TESS questionnaire.

3. STUDY DESIGN

Type of Design

This is a prospective phase III, multicentre, randomised controlled clinical trial.

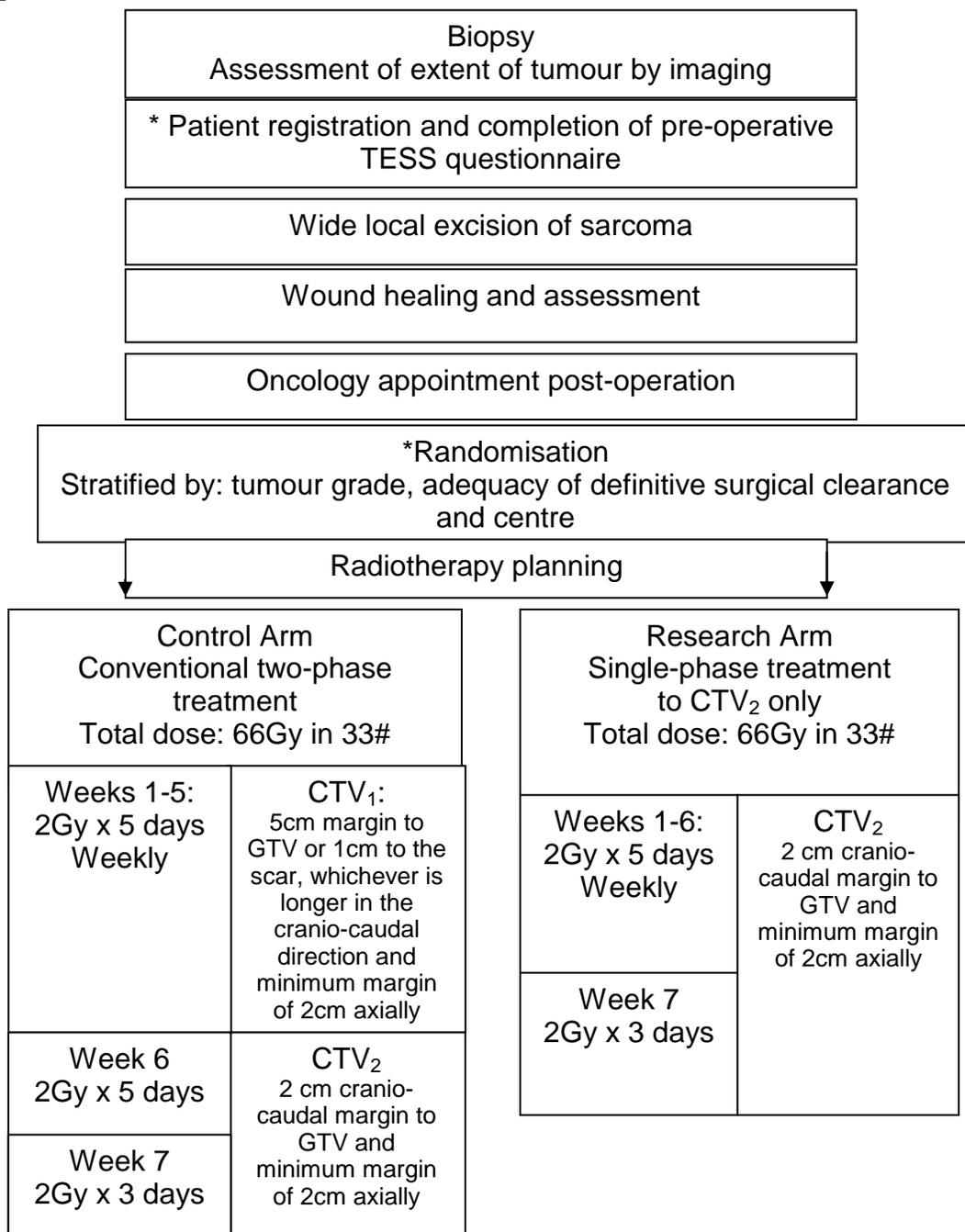
Patients will be required to give informed consent twice: at registration and randomisation.

Patients will be registered into the trial prior to surgery, in order to have the initial assessments and to have the option to take part in the VORTEX-BIOBANK sub-study.

Patients will be randomised into the trial after surgery, once it has been confirmed that they are still eligible for radiotherapy treatment and the treatment options have been explained to them by a consultant oncologist/radiotherapist.

Patients must be randomised within a time frame so that trial treatment will commence within 12 weeks of surgery.

Trial Schema



*Patient Registration and TESS completion after written informed consent obtained

** Patient to be randomised in order for protocol treatment (radiotherapy) to begin within 12 weeks of surgery

CTV: Clinical Target Volume

Schedule of Events

	Pre-op	Surgery	Post-op Assessment Upon Discharge ♦	Post-op Oncology Appointment ♦♦	RT treatment: weekly during Weeks 1-7	3 months post-op	6 months post-op	9 months post-op	12 months post-op	15 months post-op	18 months post-op	21 months post-op	24 months post-op	6 monthly Follow-up (24 months to 5 years)	Annual Follow-up (5 Years onwards)
WHO Performance Status	X	-	-	-	X	X	X	X	X	X	X	X	X	X	X
Acute Skin Morbidity Assessment	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-
Wound Assessment	-	-	X	X	X	X	X	-	-	-	-	-	-	-	-
Late Radiation Morbidity Assessment	-	-	-	-	-	-	X	X	X	X	X	X	X	X	X
Haematology (FBC Differential)	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chest X-ray	X	-	-	-	-	X	X	X	X	X	X	X	X	X	X
CT Scan Thorax ♦♦♦	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MRI Local site ♦♦♦	X	-	-	-	-	-	-	-	X	-	-	-	X	-	-
TESS	X	-	-	X	-	X	X	-	X	-	X	-	X	-	-
Patient Perceived Change of Status	-	-	-	X	-	X	X	-	X	-	X	-	X	-	-
2 X 10ml blood samples ♦♦♦♦	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-
Tumour and normal tissue samples ♦♦♦♦	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-

♦Assessment upon discharge between 24 hours and 1-week post surgery dependant on severity and level of surgery required

♦♦First Post-op Oncology Appointment - approximately 4-6 weeks after discharge but to be carried out according to local policy

♦♦♦And additionally if required by clinical suspicion

♦♦♦♦ Only patients participating in the Translational Research

Toronto Extremity Salvage Score

The Toronto Extremity Salvage Score (TESS) is a patient-completed measure of physical disability (Davis *et al*; 2004) that is, reflecting patient's ratings of the difficulty experienced in activities of daily living, including self-care, mobility and role functions. The Toronto Extremity Salvage Score ranges from 0 to 100 and higher scores reflect better function.

Recruitment

The trial aims to complete recruitment of 400 patients within 4 years. The trial will open to recruitment in March 2006 with expected completion of recruitment by March 2010. Patients will be recruited from the main cancer centres in the UK that treat these diseases. We should aim to recruit 100 patients per year.

4. ELIGIBILITY CRITERIA

Inclusion Criteria

Patients who fulfil all of the following criteria are eligible for the study:

- a) Histologically proven soft tissue sarcoma. Imaging and pathology from first surgery are required.
- b) Lesion originates in extremity. For upper extremity this includes lesions from the medial border of the scapula to tumours as far distal as the finger tips. It does not include lesions of the chest wall arising adjacent to the scapula but not originating in the shoulder bone. The lower extremity regions include hip girdle tumours commencing at the iliac crest, excluding lesions arising from within the pelvis and extends to include lesions as far distal as the toes.
- c) The patients who have undergone excisional biopsy with positive margins or other inadequate surgery (macroscopically involved margins) will be eligible for entry into this study only following further definitive re-excision. A microscopically irradical surgical margin is permitted but not a macroscopically involved one. Patients with positive margins in whom no further surgery is possible short of amputation or major functional loss may be included provided there is no macroscopic residual disease.
- d) Patients with local recurrence within 3 months of previous surgery and who undergo subsequent re-excision may be included as they are considered to have initial inadequate primary excision.

- e) Adequately treated non-melanomatous carcinoma of the skin or in situ carcinoma of the cervix.
- f) Patient had prior invasive malignancy but has been disease free for at least 3 years.
- g) Patient has been evaluated by the surgeon and radiotherapist who agree that a combination of the two treatments is appropriate and that the patient is fit for protocol therapy. (The indications for adjuvant post-operative radiotherapy are given in Appendix 1)
- h) No prior radiotherapy to the local site.
- i) Signed and dated Patient Informed Consent.
- j) Protocol treatment is to begin within 12 weeks of surgery.
- k) Patient must be 16 years of age or older.
- l) All Centres should take appropriate measures to ensure that no pregnant or potentially pregnant women receive radiotherapy.
- m) Male and female patients of reproductive potential must agree to use medically acceptable contraception during the duration of radiation treatment and for three months following the completion of the radiation treatment.

Exclusion criteria

Patients who fulfil any of the following criteria are not eligible for admission to the study:

- a) Patient has rhabdomyosarcoma of the alveolar or embryonal subcategories, primitive neuro-ectodermal tumour (PNET), soft tissue Ewing's sarcoma, extraskeletal osteosarcoma, aggressive fibromatosis (desmoid tumours), dermatofibrosarcoma protruberans or Gorlin's syndrome.
- b) Patients with local recurrence after previous treatment of a sarcoma (as they have a significantly higher risk of late recurrence) or local recurrence more than 3 months after previous definitive surgery.
- c) Concurrent malignancy (except adequately treated non-melanomatous carcinoma of the skin or in situ carcinoma of the cervix).
- d) The surgery performed has left macroscopic tumour in situ.
- e) Use of neoadjuvant or adjuvant chemotherapy.
- f) Patient has regional nodal disease or unequivocal distant metastasis.
- g) Other major medical illness judged likely by the local Investigator to preclude safe administration of protocol treatment.

5. TREATMENT PLAN AND ASSESSMENTS

SURGERY

Surgical treatment is identical in both arms.

Tumour and normal tissue samples will be taken at the time of surgery from those patients that have consented to participate in the translational research.

Pre surgery assessments

- Performance Status
- Haematology (FBC with differential)
- All patients will undergo preoperative imaging with MRI, chest X-ray and CT Thorax
 - Definition of lung metastases: minimum criteria determined by spiral CT scanning are 3 or more lesions, which are 5mm in maximum diameter or a single lesion \geq 1cm. These patients will be classified as having “certain” pulmonary metastases. Scans of patients registered as having metastatic disease with fewer or smaller lesions will be classified as “possible” metastatic disease.
 - Definition of bone metastases: must include confirmation of bone scintigraphy or plain radiograph abnormalities either by MRI scan or biopsy or both.
- All patients will be registered into the VORTEX study, after giving written informed consent
- A pre-operative assessment of limb function using TESS will be carried out

Planning

The planning of surgical resection is based on the clinical evaluation of the lesion and review of the imaging. The aim will be to achieve resection without tumour present at the resection margin on gross or microscopic review whilst maximising preservation of function. In recurrent cases, the surgeon must decide whether the recurrent tumour nodule is to be excised or if the entire previous operative field will be excised.

Resection

Complete resection of the tumour and an overlying margin of normal tissue will be performed except when the tumour contacts a major nerve vessel or bone. In these cases the critical structure will be generally preserved unless it is involved by gross tumour. If surrounded by gross tumour these structures will be sacrificed and re-constructed where possible.

Assessment of resection margins

These will be evaluated for evidence of gross tumour. If gross tumour is evident this should be confirmed by a microscopic analysis.

Resection classification

The surgical margins will be clinically classified as one of the following and recorded by the surgeon at the completion of the surgical procedure as:

- Wide resection: a layer of normal tissue overlies the tumour in all dimensions.
- Radical resection: complete excision of tumour compartment
- Marginal resection: resection through “pseudocapsule” no macroscopic residual tumour
- Gross residual disease: macroscopical tumour left behind

The final operative and pathology findings will be used to assign a resection classification as follows:

R0 - Macroscopically complete tumour resection with microscopically negative surgical margins.

R1 - Macroscopically complete tumour resection with microscopically positive surgical margins

R2 - Macroscopically incomplete tumour resection (i.e. with gross residual disease)

Closure

The technique of wound closure is left to the surgeon's discretion and drains will be sited just beyond the end of the scar so that the drain tract will be included in the radiotherapy field. Surgical dissipation should be minimised as much as possible. The use of soft tissue flaps or vascularised tissue transfer techniques will be noted.

Communication between surgeon and radiotherapist

For this trial to be successful it is essential that the radiotherapist should be clearly aware of the surgical procedure that the patient has undergone so that he/she can plan the appropriate radiotherapy field.

As a matter of routine the radiotherapist should be sent the following information:

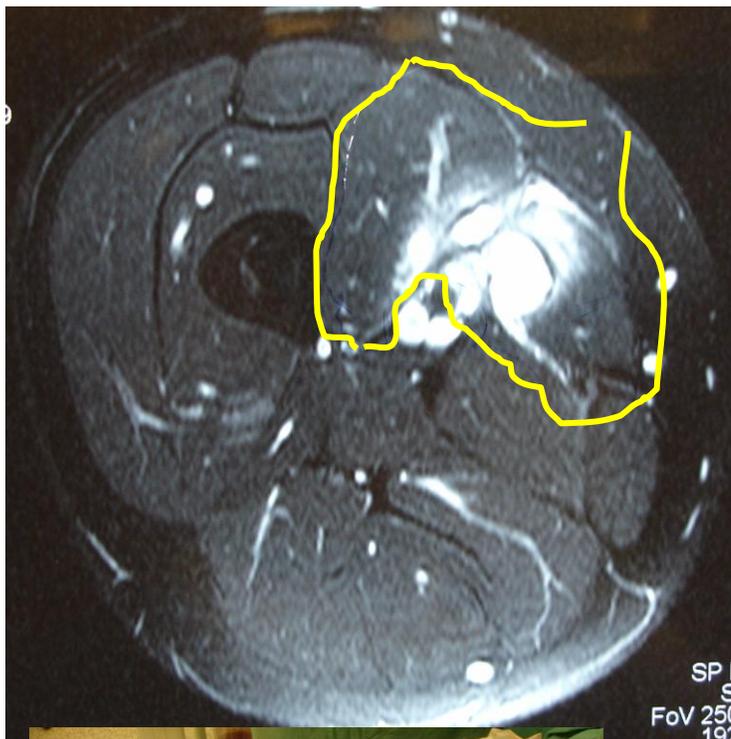
Pre operative MRI scans

Copy of typed operation note

Copy of resection histology

It may be helpful to mark the proximal, distal, medial and lateral margins of the excision bed with surgical clips – this needs to be identified to the radiotherapist as it may cause problems with subsequent CT or MRI images

We have found that one of the best ways of communicating the extent of the tumour and the resection is to send photos:



This shows the surgical route around a STS of the sartorius and vastus medialis with some extension onto the surface of the adductor magnus. The femoral vessels have been 'plucked' out from Hunter's canal from behind leaving a close – but clear margin.



The photo shows the extent of the primary tumour (cross hatched) and the resection margins compared to the scar.

Post surgery assessments

Upon discharge

- Wound assessment

First appointment with Clinical Oncologist post-operation

- Wound assessment

- Completion of the Toronto Extremity Salvage Score (TESS) questionnaire

- Completion of the Patient Perceived Change of Status questionnaire

- 2x 10 ml of blood samples will be collected from those patients that have consented to participate in the translational research.

PATHOLOGY

Pathologists and surgeons will be responsible for ensuring that the analysis of margins is performed and recorded accurately according to the nationally agreed national dataset.

Location

Each tumour will be characterised by its location, superficial or deep to the fascia of the muscle compartment of the limb. If a tumour has started subcutaneously and spread deep to fascia or vice versa this should be indicated as both deep and superficial.

Size

The surgical specimen will be measured in three dimensions and recorded in mms.

Diagnosis

The diagnosis should be based on the latest WHO text on the subject (Pathology and Genetics of Tumours of Soft Tissue and Bone. Ed. Fletcher CDM, Unni KK, Mertens F. IARC Press, Lyon, 2002.).

Tissue diagnosis will be reviewed centrally.

Assessment of grade

Grading should be done using the Trojani system as follows:

Degree of differentiation:

Well differentiated = 1

Intermediate = 2

Poorly differentiated = 3

Mitoses per 10 hpf:

0 – 9 = 1

10-19 = 2

>10 = 3

Necrosis

Nil = 0

<50% = 1

>50% = 2

The scores are then added and graded as follows:

Score 2 or 3 = Grade 1

Score 4 or 5 = Grade 2

Score 6+ = Grade 3

Nature of margin

Please record whether the margin of the tumour is 'pushing', 'infiltrative' or 'multifocal' And also if there is vascular invasion.

Margins

Please record the closest margin in mm and the nature of tissue at that margin (e.g., muscle, fascia, periosteum)

RADIOTHERAPY

Radiotherapy Planning

Treatment plans will be customised to the individual case and will depend on the specific anatomic site and location of the primary tumour and any prior surgical procedures including biopsy.

Local extremity immobilisation will be mandatory and should be accomplished in accordance with local practice. There may be situations which do not require immobilisation i.e. scapula. Patients will undergo a CT planning scan to define the target volumes. Immobilisation will be surveyed as part of verification and repeatability study in quality control program.

The treatment plan will be simulated and documented with simulation portal films prior to the start of treatment. Patient position during planning, simulation and treatment must remain constant. Immobilisation devices used should be specified. The reproducibility of the position will be assessed by orthogonal laser beams and portal images.

Bolus should not be used except in situations where the skin is within the target volume.

The following should be taken into consideration in the radiotherapy planning:

- There is a risk of bone fracture above 60Gy, therefore when contouring a corridor of bone adjacent to CTV must be preserved to reduce fracture.
- Arm sarcomas:
 - Immobilisation varies
 - CT problems for selected areas of the arm (upper region). If CT data does not exist the patient will have to be excluded from the trial, since this is a volume study
- Foot sarcomas:
 - CT foot as localisation
 - Try and minimise dose to sole of foot and Achilles (≤ 50 Gy)
 - Where sole of foot is part of GTV it cannot be shielded. Where it is part of expanded CTV this may be compromised at clinician's discretion

Quality assurance

In this multi-centre randomised trial the quality assurance programme (see Appendix 6) will enable confirmation that technical guidelines within the protocol have been understood and implemented correctly by participants. The programme will ensure the dose prescription is delivered according to protocol and participants will include the appropriate documentation of technique and patient related data. This will ensure that clinical observations in terms of tumour control and normal tissue damage reflect differences in the randomised schedules rather than departures from trial protocol. Techniques used will be documented and will be available should differences in observed end points emerge.

The quality assurance programme will involve:

- a) Questionnaires, including a generic questionnaire for participant researchers new to the national trials programme and a VORTEX-specific questionnaire to be completed by all participant researchers.
- b) Volume and planning exercises to be completed by each participant researcher. The voluming exercise will be preceded by peer review and discussion at a VORTEX participant researchers meeting.

- c) Site visits to assess immobilisation techniques and delivery of dose to a site-specific tissue equivalent phantom.
- d) In-vivo dosimetry of all patients within first week of treatment.
- e) Verification of patient positioning during treatment with review of a random selection of portal images by the quality assurance team.
- f) Electronic transfer of pseudo-anonymised patient data to a central location. A random selection of these will be reviewed by the quality assurance group.

Further details can be found in Appendix 6.

Radiation treatment

Treatment will utilize external beam megavoltage photons, and/or beams of appropriate energy to achieve required dosimetry. In general this will consist of photons in the 4/6 Mv range. Treatment will commence within 12 weeks of surgery.

Target volume

Clinical information CT scan/MRI and surgical reports will be used to determine the radiotherapy target volume.

- **Gross Tumour Volume (GTV)**: the concept of a post-operative GTV is rarely addressed. However, the re-construction of the pre-operative GTV can be useful in planning radiotherapy treatment for this disease site. It is defined as the entire macroscopic demonstrable tumour present before surgical excision. Information about its extent should be taken from interrogation of pre-operative MRI's, clinical photos, pathology reports and operative notes.
- **Clinical Target Volume I (CTV₁)**: comprises the GTV with a margin for suspected microscopic disease. Biopsy sites, drain sites and the surgical scar are to be included in CTV₁. CTV₁ will include a 5 cm margin to the GTV or 1 cm to the scar, whichever is longer in the cranio-caudal direction. Axially CTV₁ will be generated by adding a minimum margin of 2 cm around the GTV unless there is an intact fascial or bony boundary.

- **Clinical Target Volume II (CTV₂)**: comprises the GTV with a reduced margin for suspected microscopic disease. No attempt will be made to encompass drain/biopsy sites or the surgical scar. CTV₂ will include a 2cm cranio-caudal margin to the GTV and an identical axial margin to CTV₁.
- **Planning Target Volume (PTV)**: includes a margin around the CTV for inaccuracies in beam and patient set-up, and for organ and patient movement. In general a 5mm margin is considered a reasonable estimate for immobilised patients and 1cm for non-immobilised patients.

Dose prescription

All doses will be prescribed as target absorbed doses according to ICRU guidelines. The dose variation should not exceed +7%/-5% within the target volumes. All fields will be treated each session.

Limiting radiation dose to critical organs

The only organs of concern in the vicinity of the radiotherapy portals are small volumes of lung and the brachial plexus in proximal extremity lesions or the small intestine in proximal lower extremity lesions. Conventional shielding should be used to minimise the dose to these organs.

If brachial plexus is in the volume, the dose should be limited to 60 Gy with dose <2 Gy in 33#. If necessary, these patients could be excluded from the final analysis.

Beam modification devices

Dose homogeneity should be achieved by use of appropriate wedges or/and tissue compensators where indicated. Shielding may be required.

Dose distribution

A transverse cross-sectional beam dose-distribution at the central axis, the proximal, and the distal limits of the target volume, as well as coronal and saggital views, should be reviewed by the treating clinician to ensure the anatomical arrangement of isodose contours around the target volume is achieved.

Randomised Treatment Arms

- **Control arm: Shrinking field technique (CTV₁ followed by CTV₂)**

A total of 33 fractions each of 2Gy should be given once a day for 5 days per week over 6 weeks and 3 days in week 7, totalling 66Gy. Treatment should not be given routinely at weekends. The first 50 Gy in 25 fractions will be given to CTV₁ and subsequent 16 Gy in 8 fractions will be delivered to CTV₂.

- **Research arm: (CTV₂ only)**

A total of 33 fractions each of 2Gy should be given once a day for 5 days per week over 6 weeks and 3 days in week 7, totalling 66Gy. Treatment should not be given routinely at weekends. The 66Gy in 33 fractions will be delivered to CTV₂ alone. No attempt will be made to include drain/biopsy sites or the surgical scar.

In the situation where a gap in treatment extends by more than 5 days, the patient should be treated as category 1 for the remainder of the treatment and will be dealt with through local protocols. Category1 should be followed by Royal College of Radiologists guidelines for management of treatment gaps.

During radiotherapy the WHO performance status, acute skin morbidity and wound assessment will be checked weekly.

Post Radiotherapy Evaluations

The aims of follow up are to detect local and or distant recurrences and to assess the treatment morbidity and its impact on limb function.

All metastatic or local recurrence should be documented and reported to the study office. The recurrence will be assessed by clinical examination at each visit and by CT or MRI where indicated.

Local recurrences must be confirmed histologically. It is vital that a detailed record – photographic and imaging (MRI) of the site of local recurrence is documented. In particular the relationship to the radiotherapy fields must be ascertained. Patient management thereafter is at the discretion of the treating clinicians.

FOLLOW-UP EVALUATIONS

3 months post –operation

- Performance Status
- Wound assessment
- Chest X-ray
- Completion of the Toronto Extremity Salvage Score (TESS) questionnaire
- Completion of the Patient perceived change of status

6 months post-operation

- Performance Status
- Late radiation morbidity
- Wound assessment
- Chest X-ray
- Completion of the Toronto Extremity Salvage Score (TESS) questionnaire
- Completion of the Patient perceived change of status

9 months post-operation

- Performance Status
- Late radiation morbidity
- Chest X-ray

12 months post-operation

- Performance Status
- Late radiation morbidity
- Chest X-ray
- MRI local site
- Completion of the Toronto Extremity Salvage Score (TESS) questionnaire
- Completion of the Patient perceived change of status

15 months post-operation

- Performance Status
- Late radiation morbidity
- Chest X-ray

18 months post-operation

- Performance Status
- Late radiation morbidity
- Chest X-ray
- Completion of the Toronto Extremity Salvage Score (TESS) questionnaire
- Completion of the Patient perceived change of status

21 months post-operation

- Performance Status
- Late radiation morbidity
- Chest X-ray

24 months post-operation

- Performance Status
- Late radiation morbidity
- Chest X-ray
- MRI local site
- Completion of the Toronto Extremity Salvage Score (TESS) questionnaire
- Completion of the Patient perceived change of status

Six monthly from 24 months to 5 years

- Performance Status
- Late radiation morbidity
- Chest X-ray

Annually from 5 years

- Performance status
- Late radiation morbidity
- Chest X-ray

6. STATISTICAL CONSIDERATIONS

Analysis of outcome measures

The primary research hypothesis for the trial is that a reduced volume of post-operative radiotherapy treatment for adult extremity soft tissue sarcomas will improve limb function without compromising local control. Secondary research hypotheses are that the reduced treatment improves toxicity, overall level of disability and is not inferior to the standard treatment in terms of disease-free survival and overall survival.

The primary analysis for the trial is to compare the experimental treatment to the control treatment in terms of benefit to limb function and non-inferiority for time to local recurrence. For limb function, TESS will be analysed using longitudinal statistical methods, in particular summary measures analysis. The two treatment groups will be compared in terms of TESS at 2 years and area under the curve using either t-tests or Wilcoxon tests depending on the distribution of the data. The proportion of patients in each treatment arm who report small, medium or large change (with worsening or improvement reported separately) between each assessment interval will be required. For time to local relapse, statistical analysis will be based on a one-sided 95% confidence interval for the hazard ratio and non-inferiority will be inferred when the entire confidence interval falls above the non-inferiority margin of 0.63 (equivalent to a difference of 80% versus 70% in 2-year local relapse-free rates).

The rates of grade 3 or 4 toxicity on the two treatment arms will be compared using chi-square tests. Overall level of disability will be analysed using longitudinal statistical methods similar to those used for TESS. Statistical analysis for disease-free survival and overall survival will be based on one-sided 95% confidence intervals for the hazard ratio to assess non-inferiority.

Interim analysis

Interim analyses will be carried out annually and presented to an independent Data Monitoring Committee (DMC). The interim analyses will present recruitment data and data on all primary and secondary outcomes.

Final analysis

The study is expected to complete recruitment within 4 years. Final analysis will be carried out after all patients have been followed up for a minimum of two years.

Calculation of sample size

Sample size calculations are based on the two primary outcome measures of limb function and time to local recurrence. In relation to limb function, a difference in TESS score between the two treatment arms of 10 points would indicate a clinical benefit to patients (Davis, personal communication). Previous data has suggested an expected standard deviation for the score of 20. The key analysis for this outcome measure is the difference in score at two years. Assuming a null hypothesis of no difference will be tested using a t-test with 5% significance level and assuming a standard deviation of 20, 105 patients per treatment arm will be needed to detect this size of difference at two years with 95% power.

In relation to local relapse, sample size is calculated based on showing that the 2-year local relapse rate on the experimental treatment arm is non-inferior to that on the control arm. The two-year local relapse-free rate on the control treatment is expected to be 80% and a decrease in this rate to 70% would be the largest difference between treatments that can be judged as clinically acceptable. A non-inferiority margin of 70% is therefore chosen as relevant for this trial. With 198 patients per arm with full follow-up for two years and using a one-sided 95% confidence interval there will be 80% power to detect non-inferiority in two-year local relapse-free rates of 10% or less.

In conclusion, with 200 patients per treatment arm, there will be 95% power to detect a difference of 10 points in the TESS score between the treatment arms at two years and 80% power to determine non-inferiority in local relapse-free rates with non-inferiority defined as a difference in two-year local relapse-free rates of 10%.

7. STRATIFICATION

Patients will be stratified by tumour grade, adequacy of surgical clearance and centre.

8. MILESTONES

The anticipated schedule is as follows:

March 2006	Open trial to recruitment
March 2010	400 patients recruited; close trial to recruitment
March 2012	Final analysis

9. SAFETY REPORTING

Definition of an Adverse Event (AE)

An Adverse Event (AE) is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Definition of a Serious Adverse Event (SAE)

An SAE is defined as any untoward and unexpected occurrence that:

- a) Results in death
- b) Is life-threatening* (at the time of the event);
- c) Requires inpatient hospitalisation or prolongation of existing hospitalisation**;
- d) Results in persistent or significant disability or incapacity;
- e) Consists of a congenital anomaly or birth defect;

*The term 'life threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Hospitalisation for pre-existing condition, including elective procedures, which has not worsened, does not constitute a serious adverse event.

NCI Common Toxicity Criteria for Adverse Events

This study will collect adverse events using the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. An electronic version may be accessed through the web at <http://ctep.cancer.gov/>. The CTCAE (Version 3.0) provides a descriptive terminology that is to be used for adverse event reporting. A grading (severity) scale is also provided in the CTCAE for each adverse event term.

Expected and Unexpected Events

The following events associated with radiation treatment are anticipated. Refer to the NCI CTCAE for grading criteria of AEs.

The following table provides the expected adverse events:

Adverse Events		
Incidence between 50%-95%	Incidence between 10%-20%	Incidence 5% or less
skeletal muscle fibrosis	moist desquamation	anorexia
erythema	lymphoedema	insufficiency fracture
epilation	dry skin	osteoporosis
pigmentation/depigmentation	nausea	radiation induced malignancy
induration	aesthesia	peripheral nerve fibrosis
Joint stiffness/immobility		brachial/sciatic nerve plexopathy
dry desquamation		diarrhoea
lethargy		tenesmus
		haematuria
		bone necrosis
		bone deformity
		anaemia
		reduced bone marrow reserve
		Bowel ulceration/perforation/stenosis
		Rectal bleeding
		frequency/dysuria/cystitis

An unexpected adverse event is any event that is not listed as an expected adverse event in the section above.

Grading of Adverse Events

The severity of each event should be graded using the CTCAE criteria, if applicable. If the event is not in the CTCAE, the following categories should be used when determining the severity of an adverse event.

- 0 No adverse event or within normal limits
- 1 Mild adverse event
- 2 Moderate adverse event
- 3 Severe adverse event
- 4 Life threatening or disabling adverse event
- 5 Fatal adverse event

Causality of Adverse Events

Attribution should be determined and reported. The following categories should be used when determining whether an adverse event is related to medical treatment or procedure:

- Definite Clearly related to investigational agent/ procedure
- Probable Likely related to investigational agent/ procedure
- Possible May be related to investigational agent/ procedure
- Unlikely Doubtfully related to investigational agent/ procedure
- Unrelated Clearly NOT related to investigational agent/ procedure

Reporting Serious Adverse Events

On becoming aware that a patient has experienced an SAE, the Investigator must ***immediately (within 24 hours):***

- ***Complete*** a SAE Form
- ***Send by fax*** the signed and dated SAE Form to the **VORTEX Study Office** along with the fax cover sheet provided in the Site Folder:

Fax: 0121 414 2230 / 4143263

A receipt of the SAE form will be faxed back to the centre within 2 working days. Please Telephone the **VORTEX Study Office** to inform the Trial Co-ordinator if a fax is not received.

☎: 0121 414 3793

- **NOTIFY** the NHS Trust as determined by local policy (there is no requirement to report SAE's to LREC unless this is part of local policy).

Documenting Serious Adverse Events

Is the responsibility of the local Investigator to assess causality, seriousness and expectedness when reporting an SAE. The Chief Investigator (or Deputy) will also independently determine the causality, seriousness and expectedness of the event. Is the responsibility of the Chief Investigator or designee to report SAEs to the main REC and DMC.

The VORTEX Study Office will send a safety report to MREC annually and copy all investigational sites.

Data Monitoring Committee

The data will be supplied to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant trials, justifies the continuing recruitment of further patients. The committee will meet one year after the trial opens and then annually thereafter until the trial closes to recruitment. The DMC may consider discontinuing the trial if the recruitment rate or data quality are unacceptable or if the trial compromises patient safety in any way. The trial would also stop early if the interim analyses showed differences between treatments in terms of local relapse that were deemed to be unacceptable to the clinical community or showed differences in limb functioning that was deemed to be convincing to the clinical community.

Follow-up of Serious Adverse Events

In the case of an SAE, the subject must be followed-up until clinical recovery is complete or until disease has stabilised. Follow-up may continue after completion of protocol treatment if necessary. Follow-up information will be noted on the SAE Form by ticking the box marked 'follow-up' and sending to the VORTEX Study Office as information becomes available. Extra annotated information and/or copies of test results should also be provided where available.

10. STUDY ORGANISATION

Registration procedure

Registration will take place prior to surgery. A registration form should be completed and the details should be phoned or faxed through to the Cancer Research UK Clinical Trials Unit, Birmingham, between 9:00 a.m. to 5:00 p.m. Monday to Friday.

☎: 0800 7317625 or 0800 371 969

Fax: 0800 328 6412

At the end of the registration procedure the patient will be allocated with a unique trial registration number (Reg.No.). The Reg.No. should be recorded on the Registration Form this should be signed and sent to the VORTEX Study Office, along with a copy of the signed patient consent form. A copy of the registration form should be filed in the Site Folder along with the original signed patient consent form.

Randomisation procedure

Randomisation will take place after surgery once it has been confirmed that the patient is still eligible for radiotherapy and within a time frame so that radiotherapy treatment can commence within 12 weeks of surgery. Details obtained at registration will be confirmed along with all eligibility criteria.

A randomisation form should be completed and the details should be phoned or faxed through to the Cancer Research UK Clinical Trials Unit, Birmingham, between 9:00 a.m. and 5:00 p.m. Monday to Friday.

☎: 0800 7317625 or 0800 371 969

Fax: 0800 328 6412

The name of the consultant directly responsible for the patient's care will be requested at randomisation. Investigators must be pre-registered with the Clinical Trials Unit before they are permitted to enrol patients on the study.

At the end of the randomisation procedure the patient will be allocated with a unique trial number (TNO). The TNO should be recorded on the randomisation form, this should be signed and sent to the VORTEX Study Office, while a copy of the form should be filed in the Site Folder.

Site responsibilities

The Principal Investigator at each participating centre has overall responsibility for the study and all patients entered into the study, but may delegate responsibility down to other members of the study team as appropriate. The Principal Investigator must ensure that all staff involved are adequately trained.

Study start-up

Centres wanting to participate in the study should contact the VORTEX study office to obtain information. The Principal Investigator should then provide the study office with the following core documents:

- The site contact details
- The Cancer Research UK Clinical Trials Unit Investigator Agreement
- All Investigators and Co-investigators will provide an up to date copy of their CV, personally signed and dated, prior to the start of the study. The CV should detail the Investigators' education, training and experience relevant to their role in the study.
- The Study Specific Commitment Statement
- Site Responsibility Sheet
- Trust approval letters

It is the Principal investigator responsibility to apply for Site Specific Assessment (SSA) for his/her individual site. Once a site has been approved the Principal Investigator will be informed by the Chief Investigator (or one of his team) that Site Specific Assessment has been granted.

Case Report Forms and Data Collection

All study data will be recorded on the Case Report Forms (CRF) provided. The CRFs must be completed and signed by the local Investigator or his designee as soon as the requested information is available and the CRF pages returned promptly to the VORTEX study office.

In all cases it remains the responsibility of the Investigator for the timing, completeness, legibility and accuracy of the Case Report Forms and he/she will retain a copy of each completed form. The Investigator will supply the VORTEX study office with any required background data from such records.

Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated by the Investigator. If it is not clear why a change has been made, an explanation should be written next to the change. Typing correction fluid should not be used. Data reported on the CRF should be consistent with the source data or the discrepancies should be explained.

To enable peer review and/or audits from Health Authorities, the Investigator must agree to keep records, including the identity of all participating subjects (sufficient information to link records, e.g. CRFs and hospital records), all original signed informed consent forms, copies of all CRFs.

These are the forms that will need to be completed and the schedule of submission:

Form	Summary of data recorded	Schedule of submission
Registration form	Patient details. Patient registration number will be assigned	Return prior to surgery
Baseline assessments form	Patient assessments including details of imaging and tumour size	Return prior to surgery
Surgical form	Details of surgery	As soon as possible after surgery
Pathology form	Pathology information	As soon as possible after receiving the pathology report
Wound assessment form	Wound status, description of any complications	As soon as the form as been completed at the scheduled time points
Acute toxicity form	Acute skin morbidity	As soon as the form has been completed at the scheduled time points
End of treatment form	Details of radiotherapy treatment	As soon as possible after completion of radiotherapy treatment
Radiotherapy form	Full details of radiotherapy planning and treatment	As soon as possible after completion of radiotherapy treatment
TESS questionnaire	Questionnaire to assess limb functionality	As soon as the form as been completed at the scheduled time points
Patient Perceived Change of Status questionnaire	Questionnaire to assess patient's function	As soon as the form as been completed at the scheduled time points
Randomisation form	Check all eligibility criteria Patient treatment and trial number are allocated	As soon as possible after randomisation

Follow-up forms	Late radiation morbidity Recurrence/metastases Survival data	At 3, 6, 9, 12, 15, 18, 21 and 24 months post-operation 6 monthly from 2 to 5 years Annually thereafter
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11. MONITORING

Participating centres will be monitored by CRCTU staff to confirm compliance with the protocol and the protection of patients' rights, as detailed in the Declaration of Helsinki. Participating centres will be monitored by checking incoming forms for compliance with the protocol, consistent data, missing data and timing. Study staff will be in regular contact with centre personnel (by phone/fax/email/letter) to check on progress and deal with any queries they may have. On site monitoring will also be undertaken. Monitoring will be carried out according to the CRCTU Monitoring Policy and the appropriate level of monitoring will be reviewed on an ongoing basis and modified accordingly. Centres may be suspended from further recruitment in the event of serious and persistent non-compliance and or/very poor recruitment.

12. ARCHIVING

Essential documents of the sponsor/trial organisers and investigators, from trials that are not to be used in regulatory submissions, should be retained for at least five years after completion of the trial. These documents should be retained for a longer period if required by the applicable regulatory requirement(s), the sponsor or the funder of the trial.

13. WITHDRAWAL

Termination of Treatment

Below are the criteria for early termination of protocol treatment:

- Observed recurrence
- Co-morbidity
- Non disease related illness
- The patient becomes pregnant or fails to use adequate birth control
- The Investigator decides that the patient should be withdrawn from the study due to toxicity

- Death
- Withdrawal of patient consent

Withdrawal of patients for any reason should be communicated to the VORTEX study office as soon as possible by telephone. Full details of the reasons for withdrawal should be recorded on the relevant CRF if clinician-initiated; otherwise a simple statement reflecting patient preference will suffice.

Please note that patients who withdraw from trial treatment will not be regarded as having withdrawn consent for ongoing data collection unless specifically specified.

14. ETHICAL CONSIDERATIONS AND REGULATORY STANDARDS

Ethical considerations

This study will be carried out in accordance with the World Medical Association (WMA) Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996) and Scotland (2000) amendments. Copies of the Declaration may be obtained by contacting the trials unit, or from the WMA website: http://www.wma.net/e/policy/17-c_e.html.

The protocol will be submitted for COREC approval prior to circulation in accordance with the new guidance. Before entering patients into the VORTEX trial, centres must gain Site Specific Assessment (SSA) and Trust Research and Development approval.

Patient informed consent

The Investigator is required to explain the nature and purpose of the study to the patient prior to study entry. Patients will be required to give informed consent twice: at registration and randomisation. The patient will first give informed consent prior to registration to have the initial assessments required for the study. After surgery, if the patient is still eligible for radiotherapy, the consultant oncologist/radiotherapist will explain the treatment options in detail and the patient will give informed consent again prior to randomisation.

It is the responsibility of the Investigator to obtain written informed consent in compliance with national requirements from each subject prior to entering the trial or, where relevant, prior to evaluating the subject's suitability for the study. The Patient Information Sheet will be available in electronic format from the VORTEX study office to enable individual hospitals to put onto their headed paper.

Patient Confidentiality

The personal data recorded on all documents will be regarded as strictly confidential. With the patient's permission, their name will be collected at randomisation. However, patients will be identified using only their unique trial number, initials, date of birth, and hospital number on all case report forms and any correspondence between the VORTEX study office and the study site.

The Investigator must maintain documents not for submission to the VORTEX study office in strict confidence. In the case of special problems and/or governmental queries, it will be necessary to have access to the complete study records, provided that patient confidentiality is protected.

The Cancer Research UK Clinical Trials Unit, Birmingham will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party.

15. SPONSORSHIP AND INDEMNITY

This is a clinician-initiated and clinician-led study with a grant provided by CR UK. All clinicians and Research Nurses working on the study will have NHS indemnity provided as per local guidelines. In terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available in the event of clinical negligence being proven. There are no special arrangements for compensation made in respect of any serious adverse events occurring through participation in the study, whether from the side effects listed, or others yet unforeseen.

The University of Sheffield will act as the main sponsor, and the University of Birmingham will be sub contracted to carry out the co-ordination of the study.

The University of Birmingham has in force a Public Liability Policy and/or Clinical Trials Policy which provides cover for 'negligent harm' and the activities here are within that coverage. No provision has been made by the University of Birmingham for indemnity in the event of a claim for non-negligent harm.

16. PUBLICATION POLICY

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, appointed from amongst the collaborators. The Cancer Research Clinical Trials Unit and all participating centres and investigators will be acknowledged in this publication. All presentations and publications relating to the trial must be authorised by the Trial Management Group.

17. TRANSLATIONAL RESEARCH: VORTEX –BIOBANK

All patients enrolled in VORTEX will be invited to participate in VORTEX-BIOBANK. Only those patients, who have consented to further research using their tumour and normal tissue samples and blood will be entered for analysis in this study. Patients have the right to participate in the VORTEX without participating in the translational research. The biobank will be established in Manchester.

Objectives

The ability to determine early in the course of treatment patients with an increased likelihood of distant metastases would highlight individuals who might benefit from early adjuvant systemic therapy.

Translational hypothesis

The translational hypothesis is that a pre-treatment tumour molecular profile (RNA or protein) will define patients with a high risk of treatment failure following surgery and post-operative radiotherapy, and that the profile could be used in a subsequent study to identify patients who might benefit from adjuvant systemic therapy such as a hypoxia targeted agent.

Secondary hypothesis

Is that a single nucleotide polymorphisms (SNPs) in candidate genes will predict patients with a high risk of radiation side-effects, specifically limb functionality (TESS) and the level of \geq grade 2 fibrosis measured using the RTOG scale.

Specimen collection and banking

- Tumour and normal tissue samples will be taken at the time of surgery and placed in RNAlater for future microarray analyses. Tumour samples will be taken in triplicate. It is envisaged that a single normal tissue sample will be obtained from at least half of the patients. Once the tumour is clamped/removed there is a 30 minutes window for sampling the tissue and submerging in the reagent i.e. RNAlater or formalin as appropriate. The theatre nurse will take the samples and place them in the microtubes.
- The microtubes containing tissue samples must remain upright, at room temperature and held overnight in a safe area prior to posting the following day to the VORTEX-BIOBANK office.
- In Manchester, the samples are logged and placed at -80°C for storage until ready to prepare the RNA microarrays.
- Tissue blocks will be requested from relevant histopathology departments. Tissue microarrays (TMAs) will be produced and stored in Manchester. A thick section will be taken for future RNA analysis. At the moment, four replicates will be taken and arrayed on 4 separate slides, but a final decision on the most appropriate method will be taken when the first arrays are made. Samples of normal tissue will be arrayed where available. As soon as TMAs have been prepared the original blocks will be returned to the originating pathology departments.
- Two 10 ml blood samples in EDTA tubes will be taken prior or in the first week of radiotherapy at Clinical Oncology departments. The blood samples will be collected for DNA analysis, this means that no processing is required. Blood will be taken in bar coded tubes and sent at room temperature in a pre-paid and pre-addressed envelope to Manchester, where they will be placed in long-term storage at -80°C .

18. REFERENCES

Barkley HT, Jr., Martin RG, Romsdahl MM, Lindberg R, Zagers GK. Treatment of soft tissue sarcomas by preoperative irradiation and conservative surgical resection. *Int J Radiat Oncol Biol Phys* 14:693-699, 1988.

Brennan M F, Hilaris B, Shiu MH, et al. Local recurrence in adult soft-tissue sarcoma – a randomised trial of brachytherapy. *Arch Surg* 1987; 122:1289-93.

Carabell SC, Goodman RL. Radiation therapy for soft tissue sarcoma. *Semi Oncol* 1981; 8:201-6.

Cleator SJ, Cottrill C, Harmer C. Pattern of local recurrence after conservative surgery and radiotherapy for soft tissue sarcoma. *Sarcoma* 2001 5; 83-88.

Collin CF, Friedrich C, Godbold J, Hajdu S, Brennan MF. Prognostic factors for local recurrence and survival in patients with localized extremity soft tissue sarcoma. *Semis Surg Oncol* 1988; 4:30-37.

Davis AM, O'Sullivan B, Turcotte R, Bell RS, Catton CN, Chabot P, Wunder J, Hammond A, Benk V, Kandel R, Goddard K, Freeman C, Sadura A, Zee B, Day A, Tu D and Pater J. Late Radiation Morbidity Following Preoperative Versus Postoperative Radiotherapy in Extremity Soft Tissue Sarcoma. Submitted to Radiotherapy and Oncology, March 2004.

Davis AM, Sennik S, Griffin AM, Wunder JS, O'Sullivan B, Catton CN, Bell RS. Predictors of functional outcomes following limb salvage surgery for lower-extremity soft tissue sarcoma. *J Surg Oncol* 2000 Apr 73:206-11.

Eilber FR, Guiliano AE, Huth J, Mirra J, Morton DL. Limb salvage for high grade soft tissue sarcomas of the extremity: experience at the University of California, Los Angeles. *Cancer Treat Symp* 1985; 3:49-57.

Fein DA, Lee WR, Lanciano RM, Corn BW, Herbert SH, Hanlon AL, Hoffman JP, Eisenberg BL, Coia LR. Management of extremity soft tissue sarcomas with limb-sparing surgery and postoperative irradiation: do total dose, overall treatment time, and the surgery-radiotherapy interval impact on local control? *Int J Radiat Oncol Biol Phys* 1995 Aug 1 42:1 125-35.

Harrison LB, Franzese F, Gaynor JJ, Brennan MF. Long-Term Results Of A Prospective Randomized Trial Of Adjuvant Brachytherapy In The Management Of Completely Resected Soft Tissue Sarcoma Of The Extremity And Superficial Trunk. *Int J Radiation Oncology Biol Phys* 1993; 27:259-265.

Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989; 10:407-415.

Lindberg RD, Martin RG, Romsdahl MM, Barkley HT. Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. *Cancer* 1981; 47:2391-7.

Millar BM, Bragg^{CM}, Conway J and Robinson MH. Investigation of the Use of Intensity Modulated Radiotherapy (IMRT) in Comparison With Conformal Radiotherapy in the Management of Soft Tissue Sarcoma, *Int J Radiat Oncol Biol Phys Vol 51, no 3, Supplement 1 p412*.

Mundt AJ, Awan A, Sibley GS, et al. Conservative surgery and adjuvant radiation therapy in the management of adult soft tissue sarcoma of the extremities: Clinical and Radiobiological results. *Int J Radiation Oncology Biol Phys 1995; 32:977-985*.

Nielsen OS, Cummings B, O'Sullivan B, Catton C, Bell RS, Fornasier VL. Preoperative and postoperative irradiation of soft tissue sarcomas: effect of radiation field size. *Int J Radiat Oncol Biol Phys 1991 Nov 21:1595-9*.

O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, Wunder J, Kandel R, Goddard K, Sadura. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet. 2002 Jun 29; 359(9325):2235-41*.

Peat BG, Bell RS, Davis A, O'Sullivan B, Mahoney J, Manktelo RT, Bowen V, Catton C, Fornasier VL, Langer F. Wound healing complications after soft-tissue sarcoma surgery. *Plast Reconstr Surg 1994; 93:980-987*.

Potter DA, Kinsella T, Glatstein E, Welsey R, White DE, Seipp CA, Chang AE, Lack EE, Costa J, Rosenberg SA. High-grade soft tissue sarcomas of the extremities. *Cancer 58:190-205, 1986*.

Robinson, M.H., Ball, A.B., Schofield, J., Fisher, C., Harmer, C.L. & Thomas, J.M. (1992). Preoperative radiotherapy for initially inoperable extremity soft tissue sarcomas. *Clin Oncol (R Coll Radiol)*, 4, 36-43.

Robinson, M.H., Spruce, L., Eeles, R., Fryatt, I., Harmer, C.L., Thomas, J.M. & Westbury, G. (1991). Limb function following conservation treatment of adult soft tissue sarcoma. *Eur J Cancer*, 27, 1567-74.

Robinson 1998 (personal communication)

Stotter AT, A'hern RP, Fisher C, Mott AF, Fallowfield ME, Westbury G. The Influence Of Local Recurrence Of Extremity Soft Tissue Sarcoma On Metastasis And Survival. *Cancer 1990; 66:1119-1129*.

Suit H. Sarcoma of soft tissues: radiation sensitivity, treatment field margins, pathological margins, and dose – on Fein et al., *IJROBP 32:969-967; 1995*.

Trovik CS. Local recurrence of soft tissue sarcoma. A Scandinavian Sarcoma Group Project. *Acta Orthop Scand Suppl 2001 Feb 72:1-31*.

Yang JC, Chang AE, Baker AR, Sindelar WF, Danforth DN, Topalian SL, DeLaney T, Glatstein E, Steinberg SM, Merino MJ, Rosenberg SA. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol 1998 Jan 16:197-203*.

19. APPENDICES

Appendix 1: Indications for radiotherapy

Appendix 2: WHO performance status

Appendix 3: RTOG/EORTC Late Radiation Morbidity Scoring Schema

Appendix 4: Toronto Extremity Salvage Score (TESS)

Appendix 5: Patient Perceive Change of Status

Appendix 6: Quality Assurance

Appendix 7: Patient Information Sheet

Appendix 8: Consent Form Part 1

Appendix 9: Consent Form Part 2

Appendix 10: GP Letter

Appendix 1: Indications for radiotherapy

Staging:

Stage I

IA= low grade, small, superficial or deep (G1-2, T1a-b, N0, M0)

IB= low grade, large, superficial or deep (G1-2, T2a-b, N0, M0)

Stage II

IIA= high grade, small, superficial or deep (G3-4, T1a-b, N0, M0)

IIB= high grade, large, superficial (G3-4, T2a, N0, M0)

Stage III

High grade, large, deep (G3-4, T2b, N0, M0)

<u>Stage</u>	<u>Surgical margin</u>	<u>Plan</u>
IA & IB	<=10mm	Re-resection or radiotherapy depending on impact of surgery on function
	>10mm	Watch policy
IIA	superficial (rare)	Surgery alone
	deep	Surgery + XRT unless intramuscular tumour with 20mm margin
IIB	rare	Surgery alone if margin >10mm; else re- resection or XRT
III		Surgery + XRT

Appendix 2: WHO Performance Status

- 0** Able to carry out all normal activity without restriction.
- 1** Restricted in physically strenuous activity but ambulatory and able to carry out light work.
- 2** Ambulatory and capable of all self-care but unable to carry out any work: up and about more than 50% of working hours.
- 3** Capable only of limited self-care; confined to bed or chair more than 50% of waking hours.
- 4** Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Appendix 3: RTOG/EORTC Late Radiation Morbidity Scoring Schema

ORGAN TISSUE	0	Grade 1	Grade 2	Grade 3	Grade 4	5
SKIN	None	Slight atrophy Pigmentation change Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	D E A T H D I R E C T L Y R E L A T E D T O R A D I A T I O N L A T E E F F E C T S
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosia) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture <10% linear reduction	Severe induration and loss of subcutaneous tissue Field contracture >10% linear measurement	Necrosis	
BONE	None	Asymptomatic No growth retardation Reduced bone density	Moderate pain or tenderness Growth retardation Irregular bone sclerosis	Severe pain or tenderness Complete arrest of bone growth Dense bone sclerosis	Necrosis/ Spontaneous fracture	
JOINT	None	Mild joint stiffness Slight limitation of movement	Moderate stiffness Intermittent or moderate joint pain Moderate limitation of movement	Severe joint stiffness Pain with severe limitation of movement	Necrosis/ Complete fixation	



Appendix 4: Toronto Extremity Salvage Score (TESS) – Lower Extremity



PATIENT DEMOGRAPHIC INFORMATION FORM

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

Please complete the following questions:

1.a. Please state your current work status:

- Employed full-time
- Employed part-time
- Unemployed
- Retired
- Student
- Disabled

1.b. If you are employed, please give your current job title:

Re-code: 1 Active 2 Sedentary

1.c. Briefly describe your leisure or recreational activities (examples: sports, gardening, reading):

Re-code: 1 Active 2 Sedentary

2.a. Are you regularly taking pain medication:

- None
- NSAIDS e.g. Ibuprofen
- Mild pain killers e.g. Paracetamol, Co-dydramol
- Strong pain killers e.g. Morphine



PATIENT DEMOGRAPHIC INFORMATION FORM

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: [][] Reg No. [][][][] TNO [][][]

2.b. Frequency of pain medication:

- Not applicable i.e. no medication
- Intermittent
- Once a day
- Twice a day
- 3 times or more a day

3. Describe the mobility or walking aid you use:

- No aid
- One cane or crutch
- Two canes
- Two crutches
- Walker
- Wheelchair
- Motorised wheelchair or scooter

4. List the factors that limit your ability to perform your everyday activities:

- None
- Pain
- Stiffness
- Fatigue
- Weakness
- Other (please specify below)

--



LOWER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: [][] Reg No. [][][][] TNO [][][]

The following questions are about activities commonly performed in daily life. Each question asks that you mark each item (as in the examples below) opposite the description that best describes your ability to perform each task during the past week. Some activities will be extremely easy for you to do, others will be extremely difficult or impossible.

EXAMPLE

Riding a bicycle is:

- 1 [] Impossible to do
2 [] Extremely difficult
3 [] Moderately difficult
4 [] A little bit difficult
5 [] Not at all difficult
99 [] This task is not applicable to me

You should choose the response "impossible to do.." if the activity is something that you normally do in your daily activities but are now unable to do because of physical limitations such as weakness, stiffness, or pain.

If you do not perform an activity as part of your normal lifestyle you would choose the response "99" to indicate that the item is not applicable.

Mark all items ensuring that you choose the description that most accurately describes your abilities in the past week.

1. Putting on a pair of trousers is:

- 1 [] Impossible to do
2 [] Extremely difficult
3 [] Moderately difficult
4 [] A little bit difficult
5 [] Not at all difficult
99 [] This task is not applicable to me



LOWER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

2. Putting on shoes is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

3. Putting on a pair of socks or stockings is:

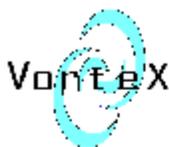
- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

4. Showering is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

5. Light household chores such as tidying and dusting are:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



LOWER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

6. Gardening is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

7. Preparing meals is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

8. Going shopping is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

9. Heavy chores such as vacuuming and moving furniture is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



LOWER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

10. Getting in and out of the bath is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

11. Getting out of bed is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

12. Rising from a chair is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

13. Kneeling is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



LOWER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

14. Bending to pick something up off the floor is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

15. Walking upstairs is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

16. Walking downstairs is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

17. Driving is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



LOWER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

18. Walking within the house is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

19. Walking outdoors is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

20. Sitting is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

21. Walking up or down hills or a ramp is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



LOWER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

22. Standing is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

23. Getting up from kneeling is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

24. Getting in and out of a car is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

25. Participating in sexual activities is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



LOWER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

26. Completing my usual duties at work is:

(work includes a job outside the home or as a home maker.)

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

27. Working my usual number of hours is:

(working includes both a job outside the home and as a homemaker.)

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

28. Participating in my usual leisure activities is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

29. Socialising with friends and family is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



LOWER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

30. Participating in my usual sporting activities is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

A. Considering all the activities in which I participate in daily life, I would rate my ability to perform these activities during the past week as:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult

B. I would rate myself as being:

- 1 Completely disabled
- 2 Severely disabled
- 3 Moderately disabled
- 4 Mildly disabled
- 5 Not at all disabled

Please comment below on any activities you find difficult to perform or on any other difficulties you experience due to the problem you currently have in your leg that you feel are important and have not been asked about in this questionnaire

Please check to make sure that you have not missed any questions.
Thank you for taking the time to answer these questions.



Appendix 4: Toronto Extremity Salvage Score (TESS) – Upper Extremity



PATIENT DEMOGRAPHIC INFORMATION FORM

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

Please complete the following questions:

1.a. Please state your current work status:

- Employed full-time
- Employed part-time
- Unemployed
- Retired
- Student
- Disabled

1.b. If you are employed, please give your current job title:

Re-code: 1 Active 2 Sedentary

1.c. Briefly describe your leisure or recreational activities (examples: sports, gardening, reading):

Re-code: 1 Active 2 Sedentary

2.a. Are you regularly taking pain medication:

- None
- NSAIDS e.g. Ibuprofen
- Mild pain killers e.g. Paracetamol, Co-dydramol
- Strong pain killers e.g. Morphine



PATIENT DEMOGRAPHIC INFORMATION FORM

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

2.b. Frequency of pain medication:

- Not applicable i.e. no medication
- Intermittent
- Once a day
- Twice a day
- 3 times or more a day

3. Are you:

- Left handed
- Right handed
- Ambidextrous

4. List the factors that limit your ability to perform your everyday activities:

- None
- Pain
- Stiffness
- Fatigue
- Weakness
- Other (please specify below)



UPPER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

The following questions are about activities commonly performed in daily life. Each question asks that you mark each item (as in the examples below) opposite the description that best describes your ability to perform each task during the past week. Some activities will be extremely easy for you to do, others will be extremely difficult or impossible.

EXAMPLE

Peeling vegetables is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

You should choose the response "impossible to do.." if the activity is **something that you normally do** in your daily activities but are **now unable to do** because of physical limitations such as weakness, stiffness, or pain.

If you do not perform an activity as part of your normal lifestyle you would choose the response "99" to indicate that the item is not applicable.

Mark all items ensuring that you choose the description that most accurately describes your abilities in the past week.

1. Putting on a pair of trousers is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



UPPER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

2. Tying shoe laces is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

3. Putting on a pair of socks or stockings is:

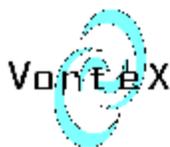
- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

4. Showering is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

5. Dressing my arms and upper body is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



UPPER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

6. Buttoning a shirt is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

7. Tying a tie or bow at the neck of a blouse is:

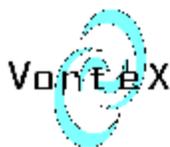
- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

8. Putting on make-up or shaving is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

9. Brushing your teeth is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



UPPER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

10. Brushing your hair is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

11. Doing light household chores is:

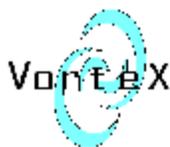
- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

12. Gardening is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

13. Preparing and serving meals is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



UPPER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

14. Cutting food while eating is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

15. Drinking from a glass is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

16. Performing heavy household chores is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

17. Going shopping is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



UPPER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

18. Giving or receiving change (i.e. coins or notes) is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

19. Carrying a shopping bag or briefcase is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

20. Lifting a box to an overhead shelf is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

21. Turning a key in lock is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



UPPER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

22. Pushing or pulling open a door is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

23. Writing is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

24. Picking up small items is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

25. Completing my usual duties at work is:
(work includes a job outside the home or as a homemaker.)

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



UPPER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

26. Working my usual number of hours is:
(working includes both a job outside the home and as a homemaker.)

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

27. Participating in my usual leisure activities is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

28. Socialising with friends and family is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me

29. Participating in my usual sporting activities is:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult
- 99 This task is not applicable to me



UPPER EXTREMITY

TORONTO EXTREMITY SALVAGE SCORE

Patient's Initials: Reg No. TNO

A. Considering all the activities in which I participate in daily life, I would rate my ability to perform these activities during the past week as:

- 1 Impossible to do
- 2 Extremely difficult
- 3 Moderately difficult
- 4 A little bit difficult
- 5 Not at all difficult

B. I would rate myself as being:

- 1 Completely disabled
- 2 Severely disabled
- 3 Moderately disabled
- 4 Mildly disabled
- 5 Not at all disabled

Please comment below on any activities you find difficult to perform or on any other difficulties you experience due to the problem you currently have in your arm that you feel are important and have not been asked about in this questionnaire

Please check to make sure that you have not missed any questions.
Thank you for taking the time to answer these questions.

Date of Form Completion:

(dd/mon/yyyy)



Appendix 5: Patient Perceived Change of Status



PATIENT PERCEIVED CHANGE OF STATUS

Patient's Initials: Reg No. TNO

Date of Birth (dd/mon/yyyy) / / Hospital No:

Hospital Name: Consultant:

Please tick appropriate box to indicate form completion point:

Post Op Oncology Appointment: 3 Month Follow Up: 6 Month Follow Up:
12 Month Follow Up: 18 Month Follow Up: 24 Month Follow Up:

Do you think there has been a change in your function since you last completed the TESS questionnaire

Please put a "X" beside the most appropriate answer

- About the same
- Better
- Worse

If you are better, how much better are you?

- 1 Almost the same, hardly any better at all
- 2 A little better
- 3 Somewhat better
- 4 Moderately better
- 5 A good deal better
- 6 A great deal better
- 7 A very great deal better

If you are worse, how much worse are you?

- 1 Almost the same, hardly any worse at all
- 2 A little worse
- 3 Somewhat worse
- 4 Moderately worse
- 5 A good deal worse
- 6 A great deal worse
- 7 A very great deal worse

Appendix 6: Quality Assurance

The quality assurance programme will follow the guidelines set out by the EORTC [1] and will be co-ordinated by the quality assurance team at Mount Vernon Hospital. The programme is aimed at detecting and assessing any deviations from what is defined in the protocol. If deviations are found corrective action, if necessary, will be taken to ensure future results are in accordance with the protocol. The programme will involve the following:

- 1) An initial generic questionnaire for all participants new to the national trials programme to gain detailed information of equipment and procedures utilised by each participating centre. A second questionnaire specific to the trial will be completed by all participants in the Vortex trial. Both questionnaires will enable the assessment of technique used in each centre prior to their becoming active in the trial.
- 2) A volume exercise will be completed by all centres wishing to enter the trial. The results of this will be discussed at a participants meeting to ensure consensus among clinicians. The exercise will involve contouring volumes of interest for three specific sites in accordance with the trial protocol.
- 3) At the initial participants meeting, as well as discussing the voluming exercise, participants will explore any issues that may arise during planning and treatment of adult patients with extremity soft tissue sarcoma. Guidelines will be established detailing delineation of volumes, planning geometry, prescription point, permitted dose homogeneity and organs at risk dose limits.
- 4) All participants will be required to re-plan an existing sarcoma patient following the protocol and guidelines agreed upon at the planning meeting. Completed plans will be anonymised and submitted for review by the quality assurance group.
- 5) A site visit by the quality assurance team at the start of the trial to validate techniques used by each centre against the protocol. Patient immobilisation will be assessed as well as dosimetric measurements within the treatment volume of a suitably shaped tissue-equivalent phantom. Results from phantom measurements will assess the capability of the treatment planning system to account for missing tissue (loss of scatter), beam obliquity and long narrow fields. Additional site visits may be necessary if there are significant changes to technique or equipment.

- 6) Under UK and EORTC recommendations [1, 2] all patients should have in-vivo dosimetry within the first week of treatment. This may be performed using semiconductor diodes, MOSFETs or thermo-luminescent dosimetry (TLD) by the participating centre. Other methods of in-vivo dosimetry should be discussed with the quality assurance team.
 - 7) Verification of patient positioning should be performed in accordance with protocol recommendations. A sample of patients will be selected at random for a verification study. Images from each patient will be collected and reviewed by the quality assurance team to assess the patient positioning and immobilisation techniques.
 - 8) All patient planning data (CT and dose data) will be anonymised and electronically transferred to a central location. Patient data selected at random will be reviewed to assess tumour coverage, organs at risk and anatomical sparing (tissue corridor).
-
1. Bolla M, Bartelink H, Garavaglia G, et al. EORTC guidelines for writing protocols for clinical trials of radiotherapy. *Radiotherapy and Oncology* 1995; 36(1): 1-8.
 2. The Royal College of Radiologists, The Society and The College of Radiographers, Institute of Physics and Engineering in Medicine. (2002) "Development and Implementation of Conformal Radiotherapy in the United Kingdom." The Royal College of Radiologists.

Appendix 7: Patient Information Sheet

PATIENT INFORMATION SHEET

VORTEX: Randomised trial of volume of post-operative radiotherapy given to adult patients with extremity soft tissue sarcoma

Dear Patient,

You are being offered the opportunity to take part in a clinical research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. It is important that you read and understand this information sheet before you decide whether or not to take part. If there is anything that is not clear or if you would like more information ask your study doctor or research nurse.

Why have I been chosen and what is the purpose of the study?

You have been invited to take part in this trial because you have recently been diagnosed with extremity (i.e. a limb, an arm or leg, sometimes applied specifically to a hand or foot) soft tissue sarcoma and your consultant has agreed that a combination of surgery and post-operative radiotherapy is appropriate for the treatment of your condition.

There is no evidence that the international practice of irradiating large volumes of normal tissue is necessary. The purpose of the VORTEX study is to assess if a reduced volume of post-operative radiotherapy given to your type of tumour will improve limb function and toxicity without increasing the risk of your cancer coming back and that this treatment is no less effective than conventional treatment in terms of survival.

Do I have to take part in the study?

Your participation in this study is entirely voluntary. You may choose not to participate or you may withdraw from the study at any time. You do not have to give any reason for your decision. Your doctor will continue to treat you with the best means available.

What would happen to me if I take part?

If you decide to take part, you will be asked to sign an informed consent form (part 1) to have the initial assessments required by the trial (detailed below) and to be registered into the trial.

Baseline assessments prior to surgery:

- Performance Status: This is a scale doctors use to describe how well you are.
- Haematology (Full Blood Count)
- Chest X-ray
- CT scan thorax: 'Computerised Tomography' scan: The CT scanner is a doughnut-shaped machine that uses advanced x-ray technology to take pictures of sections of your body, called "slices." The CT scan can reveal some soft-tissue and other structures that cannot even be seen in conventional X-rays.
- MRI scan of the local site: 'Magnetic Resonance Imaging': This is a scan of the body which uses magnetic energy to view body parts, especially useful for viewing soft tissue. MRI scans can be used to accurately detect and locate tumours and to determine if a tumour has spread.

-Completion of the 'Toronto Extremity Salvage Score' (TESS) questionnaire: This is a questionnaire to be completed by you to measure physical disability.

Post surgery (upon discharge) assessments:

-Wound assessment

First appointment with Clinical Oncologist post-operation:

-Wound assessment

-Completion of the 'Toronto Extremity Salvage Score' (TESS) questionnaire

-Completion of the 'Patient perceived change of status' questionnaire: This is a questionnaire to be completed by you to assess your change in well-being.

After your surgery, the radiotherapy treatment will be explained to you by your doctor and if you wish to continue with the study, you will be asked to sign another informed consent form (part 2) and you will be randomised to one of the two radiotherapy treatment schedules:

Control arm

Conventional radiotherapy treatment given over 33 days (5 days per week over 6 weeks and 3 days in week 7)
Total dose: 66Gy

Research arm

Conventional radiotherapy treatment dose given to a reduced volume over 33 days (5 days per week over 6 weeks and 3 days in week 7)
Total dose: 66Gy

Radiotherapy is a treatment that involves directing high-energy waves in the form of beams at cancer cells in order to kill them and so they can no longer increase in size or number. The most common way to do this is to point several beams at the tumour from a machine called a linear accelerator. This is the way radiotherapy will be given on this study.

The treatment you are allocated will be decided by a process called randomisation, and not chosen by you or your doctor. Randomisation is performed using a computer and allocates treatment rather like the toss of a coin. Randomisation is the only way that we obtain unbiased and trustworthy results.

Randomisation into the trial will take place after surgery and within a period of time so that radiotherapy treatment can commence within 12 weeks of surgery. Patients who fulfill all the eligibility criteria, will then be randomised by the Cancer Research Clinical Trials Unit (CRCTU) into one of the two treatment arms.

If you take part in this study and are in either study group, you will have the following tests and assessments:

Radiotherapy planning

When you have radiotherapy, your treatment needs to be planned carefully. This is to make sure that the treatment area includes all the cancer and avoids healthy tissue.

Radiotherapy treatment

During your treatment with radiotherapy the following assessments will be done weekly:

-Performance Status

-Wound assessment

-Acute skin morbidity assessment: This assessment will look at changes in your skin during the radiotherapy treatment.

Follow-up assessments:

Occur at 3, 6, 9, 12, 15, 18, 21, 24 months post-operation and include the following:

-Performance Status

-Wound assessment (only at 3 and 6 months)

-Late radiation morbidity (not done at 3 months): This assessment will look at changes in your skin, bones, joints and soft tissue after the radiotherapy treatment has been completed.

-Chest X-ray

-Completion of the Toronto Extremity Salvage Score (TESS) questionnaire and the Patient perceived change of status questionnaire (3, 6, 12, 18 and 24 months only)

An MRI scan will be performed at 12 and 24 months

Six monthly from 2 years to 5 years and annually thereafter:

- Performance Status

- Late radiation morbidity

-Chest X-ray

What are the side effects of any treatment received when taking part?

As well as benefits, there are side effects associated with all radiotherapy schedules. You should discuss the side effects with your study doctor. The most frequent side effects are listed below, but will be different from person to person.

Hair loss (only in the area being treated)	Fibrosis: formation of scar-like tissue in the treated area
Redness of the skin (in treatment area)	Induration: hardening of soft tissue.
Joint stiffness/ immobility	Oedema: swelling of tissue due to accumulation of excess fluid
Dryness, itching, scaling, flaking, and peeling of the skin	Tiredness
Pigmentation/depigmentation of the skin	

You should not become pregnant before or during radiotherapy because radiotherapy may injure the foetus, especially in the first three months of a pregnancy. Please discuss with your doctor if you think you may be pregnant.

Some doctors advise men against fathering a child during radiotherapy and for a few months afterwards as this could affect the number of sperm and their effectiveness. Again, your doctor will be able to discuss this with you.

Male and female patients of reproductive potential must agree to use medically acceptable contraception during the duration of radiation treatment and for three months following the completion of the radiation treatment.

Are there alternative treatments?

If you choose not to participate you will be given a treatment according to the current standard practice of your cancer centre.

What are the benefits of this research?

If you agree to take part in this study and if you happen to be in the research arm, this treatment may reduce the side effects from the radiotherapy and improve limb function or you may not gain any additional benefits compared with standard treatment. We hope that the information gained from this study will benefit patients with this type of tumours in the future.

Who is organising and funding the research?

VORTEX is a clinician initiated and clinician-led study. The study is being organised and run by the Cancer Research Clinical Trials Unit (CRCTU) at the University of Birmingham. The running costs of the trial are met by funding from Cancer Research UK. Your doctor will not receive any personal financial payment for including you in the VORTEX study.

Will I be paid for taking part?

You will not be compensated for taking part in this study.

What if I choose to leave the study?

If you decide to withdraw from the VORTEX study we would still like to continue to collect information about your progress from your medical records so as not to affect the overall quality of the trial data. If you have any objection to this please let your doctor know when you withdraw from the study. Data collected prior to withdrawal will be kept and analysed.

Will my taking part in this study be kept confidential?

All your details will be treated as strictly confidential and will be covered under the Data Protection Act 1998. Your doctor with your permission will supply your name, date of birth, hospital number and NHS number to the CRCTU when s/he registers you on the study along with a copy of the complete consent form to ensure adequate consent was given.

After this, to preserve your anonymity, all other information about you which leaves the hospital will refer to you only by a unique trial number allocated to you, your initials and/or by your date of birth and hospital number.

All information will be securely stored, in both electronic format and paper at the CRCTU, and will only be accessible by authorised personnel.

With your consent your GP will be informed that you are taking part in the study and we may ask her/him to provide information on your progress. If we do need to contact your GP for



any follow-up information, we will need to use your full name in our correspondence if you have agreed to provide this.

Occasionally we may need to check your medical records to make sure that the information provided about you is accurate. This will be done by clinical staff or designated CRCTU personnel. Government regulatory agencies may also require access to your medical records to ensure that the trial is being run in accordance with UK law. Under no circumstances will you be identified in any way in any report arising from the study.

After your treatment we will continue to contact your hospital to find out how you are. We know that it is possible for patients to lose touch with their hospital. If this happens we will still need to be able to collect important basic details of your progress. The Office of National Statistics (ONS) keeps records that can easily provide the information we need. With your consent the ONS will pass on this information to the CRCTU if required. Any information received in this way remains confidential and is used only for the purpose of the study.

What if I want more information?

You will be given a copy of this information sheet and the signed copy of the consent form for you to keep. Please feel free to ask any further questions of the doctors and nurses looking after you before deciding to take part in the trial or at any time during the study. Before you make a decision, you may want to discuss the study with your family and friends and with your family doctor.

Doctor **Telephone No:**.....

Study Nurse **Telephone No:**.....

If you prefer you can contact CancerBACUP (an independent patient advisory group):

**Freephone: 0808 800 1234 Address BACUP: 3 Bath Place
Rivington Street
London EC2A 3JR**

Or visit their website at <http://www.cancerbacup.org.uk>.

Please take as much time as you need to make a decision and then let your doctor know what you have decided so that your treatment can be arranged.

Thank you for taking time to read this leaflet and considering taking part in this study.

Appendix 8: Patient Consent Forms

VORTEX Study

PATIENT CONSENT FORM

Part 1

- I confirm that I have read and understood the Patient Information Sheet (version 4 dated 2nd August 2010) for the VORTEX study and have had the opportunity to ask questions and discuss the study.
- I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected.
- I understand that sections of my medical notes which identify me by name may be looked at by responsible individuals, from the Clinical Trials Unit or from government regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. However, I understand that I will not be identified by name in any reports or publications resulting from this study.
- I give permission for my full name, date of birth, hospital number, NHS number and a copy of this consent form to be given to the Clinical Trials Unit when I am registered on the trial. I understand that all data collected about me will be held under the provisions of the 1998 Data Protection Act and will be stored in manual and electronic files in secured encoded format.
- I agree to have the initial assessments required by the study.
- I agree to take part in the VORTEX study.

Name of Patient	Date	Signature
Name of Person taking consent (if different from Investigator)	Date	Signature
Name of Investigator	Date	Signature
Name of Witness	Date	Signature

Original to be kept with Investigator Site File or hospital notes, 1 copy for patient, 1 copy for VORTEX Study Office



VORTEX Study

PATIENT CONSENT FORM

Part 2

- I confirm that I have read and understood the Patient Information Sheet (version 4 dated 2nd August 2010) for the VORTEX study and have had the opportunity to ask questions and discuss the study.
- I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected.
- I give permission for a copy of this consent form to be given to the Clinical Trials Unit when I am randomised on the trial.
- I give permission for my GP and other medical personnel treating me to be informed of my participation in this study and sent details of the trial.
- I understand that sections of my medical notes which identify me by name may be looked at by responsible individuals, from the Clinical Trials Unit or from government regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. However, I understand that I will not be identified by name in any reports or publications resulting from this study.
- If I choose to withdraw from the trial, I give my permission for my doctor to continue to provide the Clinical Trials Unit with basic information that would routinely be collected about me and recorded in my medical notes. I am aware that I can also withdraw this consent should I choose to withdraw from the trial.
- If necessary, I give permission for information about my progress to be obtained from my GP or through the Office for National Statistics, and understand that this will be done using my full name and/or NHS number.
- I agree to take part in the VORTEX study.

Name of Patient	Date	Signature
Name of Person taking consent (if different from Investigator)	Date	Signature
Name of Investigator	Date	Signature
Name of Witness	Date	Signature

Original to be kept with Investigator Site File or hospital notes, 1 copy for patient, 1 copy for VORTEX Study Office



Appendix 9: GP Notification Letter

GP Notification letter

VORTEX Study: Randomised trial of volume of post-operative radiotherapy given to adult patients with extremity soft tissue sarcoma

Dear Dr.

Your patient _____ has been diagnosed with extremity soft tissue sarcoma and has agreed to take part in the VORTEX clinical trial.

This is a prospective phase III multicentre randomised controlled clinical trial. The study is being co-ordinated by the Cancer Research UK Clinical Trials Unit (CRCTU) at the University of Birmingham.

The objective of the VORTEX trial is to assess if a reduced volume of post-operative radiotherapy increases limb function without compromising local control. An analysis of the association between dose, volumes irradiated and morbidity and functional outcome will be carried out.

A translational research study will be performed as part of the VORTEX trial. This study will involve collection of tumour and normal tissue samples at the time of surgery, which will be used for future microarray analyses.

Also, blood samples will be taken prior to radiotherapy and these samples will be used for a future genetic study. Only those patients, who have consented to further research using their tumour and normal tissue samples and blood, will be entered for analysis in this study. Patients have the right to participate in the VORTEX trial without participating in the translational research.

Your patient has been provided with an information sheet for the trial (copy enclosed) which explains why s/he has been approached to take part in the trial, that the participation is entirely voluntary, and emphasises that they are free to withdraw from the trial at any time without prejudicing their future medical care.

Should you have any questions or require further information about this research, please do not hesitate to contact the nurse or doctor in charge of the local study.

Your contact:

Tel:

You may also contact the VORTEX Study Office:

Tel: 0121 4143793

E-mail: VORTEX@trials.bham.ac.uk

Kind regards

Yours sincerely

Enc. VORTEX Patient Information Sheet