FaR-RMS

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

Version
2.0c
21-Mar-2024

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EPSSG European Paediatric Soft Tissue Sarcoma Study Group

CONTENTS

Table of Figures

List of Tables

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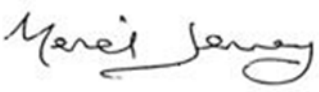
SIGNATURE PAGE

FaR-RMS Trial Protocol Version 2.0c version date 21-Mar-2024

This protocol has been approved by:

Name:	Prof Meriel Jenney	**Trial Role:**	Chief Investigator
Signature:		**Date:**	09-Apr-2024

This protocol describes the FaR-RMS trial and provides information about procedures for patients taking part in the FaR-RMS trial. The protocol should not be used as a guide for treatment of patients not taking part in the FaR-RMS trial.

The clinical trial will be conducted in compliance with the protocol

AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version:

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1		1.0b	Non Substantial	Addition of NCCs for Israel, Australia and New Zealand. Addition of new coordinating staff Updated radiotherapy trial schema to make it clearer that patients can also enter directly at RT1B Clarification over risk assignment timepoints. Clarification that cefixime or equivalent is recommended for prophylaxis & timing Clarification that the relapse question is not currently open to recruitment Clarification over nodal stage Clarification over how patients should be risk assigned when tumour size is not evaluable Clarification over FDG-PET substudy imaging. Clarification that Dexrazoxane is permissible supportive care treatment Clarification over relapse section Correction of the following errors: Correction of small typographical errors Missing Oberlin score criteria added to figure three, in line with the criteria in the inclusion/exclusion criteria Correction of PTV definition Correction of Dutch NCC Name Clarification of definition of Local failure free survival (LFFS) and loco-regional failure free survival (LRFFS) Clarification of the Acute post-radiotherapy complications and Late local therapy complications which should be collected from the beginning of treatment, not the end. Correction of typographical error – patients are assessed after 3 cycles of induction chemotherapy, not two, as per standard.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
				Correction of wording regarding radiotherapy timing Correction of wording for radiotherapy to patients with an Unresectable incomplete response (to induction chemotherapy) HLFR Escalated dose Corrected guidance for SAEs during phase 1b and radiotherapy Correction of chemotherapy flow charts in appendices Correction regarding the age ranges in the QoL questionnaire. Correction of errors in minimisation factors. Correction to ensure reference to PET scoring via Deauville criteria is consistent throughout.
2		2.0a	Substantial	Revised design of relapse question (CT3): VI_RT now standard of care and question updated to VI_RT Vs VI_RR (regorafenib) • Additional inclusion criteria to reflect new drug regimen • Additional secondary and exploratory endpoints added • Clarification of minimum sample size • Extended follow-up duration • Background and rationale updated • Regorafenib added as new IMP (tablets and granules) • Revised Schedule of Assessments for relapsed patients to reflect new drug regimen • VI_RR treatment regimen added • New dose modifications for regorafenib • Addition of further information regarding timing of local therapy in relapse • Addition of biological sample collection and studies • Addition of DW-MRI biomarker study • Additional warning added regarding use of neomycin with regorafenib • Additional prohibited medications when taking regorafenib • Enhanced data collection: collection of all AEs (including causality) and concomitant medications. • All SAEs will be reported in expedited manner (expected SAR section will not apply) • Updated minimisation factors • Clarification of decision guidelines • Information regarding provision of free regorafenib and funding by Bayer. Also, data in the relapse study will be provided to Bayer. Clarification of time points of potential study entry

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
				RT1[A] – clarification of inclusion criteria PET-Sub-Study- OS added as secondary endpoint Risk-Benefit Assessment added Addition of COVID 19 Risk Assessment Lifestyle Guidelines updated to include definition of 'woman of childbearing potential' and instruction 'men must refrain from donating sperm for 6 months after receiving the last dose of study treatment.' Instruction added to re-informed that suspected DLTs must be reported immediately Clarification that timings and routes of administration may be as per local practice – with recommendations still provided. Vincristine recommendation changed to short infusion Clarification of definition of DLT Updates to 'Schedule of Assessments for new diagnosed frontline patient' • Clarification that protocol defined assessment in maintenance commence at the point of CT2[A] and CT2[B]. • Pregnancy monitoring should continue for a 12 months after last treatment • (e)GFR and Tubular Function – should be monitored more frequently in patients with impaired renal function • Clarified Staging Investigations Clarified assessments for patients participating in CT2[A] and CT2[B]. Clarifications in dose modification and supportive care sections Updated Dose capping section Additional preservation of fertility information including 'men must refrain from donating sperm for 6 months after receiving the last dose of study treatment'

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
				Updated 'Definitions of Response' to add in missing permutations and to include lymph node response. Addition of linked-DW-MRI sub-study in frontline patients Addition of optional bio -banking Clarification that Sponsor will monitor specificity, frequency or severity of SAEs Clarification of as to where SUSARs will be reported Clarification that all adverse events must be recorded in the patient's notes Updated to 'Details of all ARs and SAEs (except those listed) will be documented and reported from the date of registration/randomisation in to a treatment question Correction of AE terminology Clarification that eRDE training will be documented Addition that on-site monitoring may be performed by a 3rd party contract research organisation Addition of how missing data will be dealt with Updated Trial Organisational Structure figure to reflect text Updated 'Dose Modifications for Infants 6-12 MONTHS AND/OR < 10 KG' to include vincristine on Day 8 in I_RIVA schedule Addition of Appendix : Biological Studies Endpoints Addition of Appendix (subgroups B and C) : Definitions of Sites Addition of Appendix : Biological Studies Endpoints Addition of Appendix : DW-MRI Guidelines Administrative updates:

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
				• Addition of clinicaltrials.gov number • Inclusion of the FaR-RMS electronic remote data capture system address. • Updates to personnel details • Clarification that amendment to add any new IMP will be submitted to each competent authority • Updated /clarified figures • Updated abbreviations • Correction of typographical errors • Updated EpSSG Guideline links Note: these amendments include those made at the request of participating countries' competent authorities
3		2.0b		**In response to MHRA non acceptance of protocol 2.0a** Clarification of Regorafenib discontinuation for the following conditions - Steven Johnson's Syndrome - Toxic epidermal necrolysis - PRES Addition of hepatotoxicity monitoring for Regorafenib Coagulation monitoring for participants predisposed to bleeding
4	21-Mar-2024	2.0c	Non-substantial	**Non-substantial amendments:** **Administrative updates:** Trial Details: Confirmation of EU CT number: 2024-510579-40-00 Changes to personnel in Trial Management Group. Changes to personnel in Coordinating Centres. <u>Protocol Signature page</u>: Clarification that the clinical trial will be conducted in compliance with the protocol. **Trial Synopsis:** Confirmation that phase 1b recruitment is complete. Font colour changed to indicate phase 1b recruitment is complete.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
				Cross reference to definition of sites added to radiotherapy sections. Previously mentioned in Appendix 18 only. <u>Abbreviations:</u> Previously undefined abbreviation added (FSH) <u>Lifestyle guidelines:</u> Clarification of contraceptive advice for males. <u>Procedure for Online Study Entry, Randomisation and Registration</u> Update to database web address. <u>Phase 1b combination dose finding:</u> Confirmation that phase 1b recruitment is complete. Font colour changed to indicate phase 1b recruitment is complete. FRONTLINE (NEWLY DIAGNOSED) PATIENTS Cross reference added to clarify that CT1 patients will be dosed in mg/kg – already defined in Appendix 4 Cross reference added to dose capping advice. Cross reference to dose modifications Confirmation of irinotecan dose in CT1 as per DMC recommendation in Phase 1b section. Clarification of wording around dose adjustments in maintenance <u>RELAPSED RMS – CT3</u> Correction of Thyroid function tests Correction of FSH timepoint Correction of sample tubes used. SUPPORTIVE CARE Clarification of existing advice on ARDS and HFI PROHIBITED CONCOMITANT MEDICATION

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
				Confirmation of exclusion criteria that other anti-cancer IMPs cannot be give concomitantly. Correction of prohibition of neuromuscular blocking agents RADIOTHERAPY Cross reference to definition of sites added to radiotherapy sections. Previously mentioned in Appendix 18 only. FDG PET SUB-STUDY Correction of documentation cross referenced. PATIENT FOLLOW-UP Reference to standard of care guidelines added. Information from trial synopsis coped to follow-up section (cross reference) ADVERSE EVENT REPORTING Correction to placement of wording on events that are reported as expected. Correction of SAE reporting details to show email is preferred method f reporting. Update to fax number. Correction of common toxicities table Throughout: Corrections to spelling and grammar. Update of dactinomycin to actinomycin D for consistency Updated bookmarks where incorrect sections referenced. Updates to wording to retain protocol consistency.

TRIAL SYNOPSIS

Title
An overarching study for children and adults with Frontline and Relapsed RhabdoMyoSarcoma (RMS)

Acronym
FaR-RMS

Trial Design
FaR-RMS is an over-arching study for patients with newly diagnosed and relapsed RMS including multi-arm, multi-stage questions with three principal aims. These are to evaluate:

- systemic therapy through the introduction of new agent regimens in the most advanced disease states: Very High Risk (VHR), High Risk (HR) and Relapse
- the duration of maintenance therapy
- radiotherapy to improve local control in VHR, HR and Standard Risk (SR) patients and to treat metastatic disease.

In addition the study will evaluate:

- risk stratification through the use of *PAX-FOXO1* fusion gene status instead of histological subtyping.
- the use of FDG PET-CT response assessment as a prognostic biomarker for outcome following induction chemotherapy

FaR-RMS includes a study entry point where all patients with RMS may give consent for the analysis of their biological samples and tumour pathology, alongside the collection of very basic patient characteristics, a treatment summary, and follow-up data for events.

Newly diagnosed patients should where possible be entered into the FaR-RMS study at the time of first diagnosis prior to receiving any chemotherapy. However, patients can also be entered at the point of radiotherapy, maintenance or relapse randomisations. Exceptionally, patients may be entered at any other time point. Eligible patients with VHR, HR, SR and relapsed disease can be offered entry in to the relevant trial questions. Patients may be entered into more than one randomisation/registration following study entry. Separate consent is required for study entry and for each trial question.

Not all trial questions will be open to recruitment at any one time.

FaR-RMS is intended to be a rolling programme of research with new treatment arms being introduced dependant on emerging data and innovation, provided it is within the pre-defined research remit of the trial. A maximum of three new arms will be added to each of the frontline (VHR and HR) and relapse randomisations; and a maximum of four new arms to the Phase 1b component. An application for substantial amendment will be submitted to each competent authority for approval before addition of any new Investigational Medicinal Products (IMPs).

Trial component	**Entry type**	**Patient risk group** See Table 3: Risk Group Assignment	**Comment**
FaR-RMS biology	Study entry (all patients at first point of study entry – i.e. at diagnosis or maintenance or relapse)	All RMS patients	
Phase Ib	Registration	VHR	New Phase 1b arms may include VHR and/or relapse patients.
Front line chemotherapy randomisations	Randomisation	VHR, HR	To open following completion of I_RIVA Phase 1b dose-finding study
Maintenance chemotherapy randomisations	Randomisation	VHR, HR	Randomisation takes place at end of 'standard' maintenance therapy
Radiotherapy randomisations	Randomisation	VHR, HR, SR	
Relapse randomisations	Randomisation	Relapse	

Objectives

Primary Objectives

Phase I Dose Finding Studies

- To determine the recommended phase II dose (RP2D) of new systemic therapy regimens.
    - The first combination to be tested is irinotecan in combination with ifosfamide, vincristine and actinomycin D (I_RIVA)

Frontline Chemotherapy Questions

- To compare systemic therapy regimens for patients with VHR disease at diagnosis (**CT1^{A}**).
    - The first new combination regimens to be compared are IVADo and I$_R$IVA in a dose intense schedule.
- To compare new systemic therapy regimens with standard chemotherapy for patients with HR disease at diagnosis (**CT1^{B}**). The standard chemotherapy is ifosfamide, vincristine, actinomycin D (IVA) (**CT1^{B}**).
    - The first new combination regime to be compared is irinotecan combined with IVA (I$_R$IVA) in a dose intense schedule.

Radiotherapy Questions

- To determine whether pre-operative or standard post-operative radiotherapy is better for patients with resectable disease (**RT1^{A}**)
- To determine whether dose escalation of radiotherapy improves the outcome in patients with a higher local failure risk (**RT1$^{B/C}$**)
- To determine whether radiotherapy treatment of all sites of disease, including metastatic sites, when compared to radiotherapy treatment to the primary site and involved regional lymph nodes alone, improves the outcome for patients with unfavourable metastatic disease (**RT2**)

Maintenance Chemotherapy Questions

- To determine whether the addition of a further 12 cycles of vinorelbine and cyclophosphamide (VnC) to standard 12 cycles of maintenance chemotherapy (i.e. 24 cycles total) improves the outcome for patients with VHR disease at diagnosis (**CT2^{A}**)
- To determine whether the addition of a further 6 cycles of VnC (intravenous (i.v.) vinorelbine, oral cyclophosphamide) to the standard 6 cycles (i.e. 12 cycles total) improves the outcome for patients with localised HR disease at diagnosis (**CT2^{B}**)

Relapsed RMS Question

- To determine whether new systemic therapy regimens improve event free survival in relapsed RMS compared to standard therapy (VI$_R$T) (**CT3**):

  Initial new systemic therapy combination to be tested:
    - Regorafenib (R) added to vincristine and irinotecan (VI$_R$) (VI$_R$R)

Main Overarching Secondary Objectives

- To validate whether the use of fusion status (PAX3/PAX7-FOXO1) in place of histopathological diagnosis improves risk stratification.
- To determine whether assessment of fusion status is necessary in tumours classified as Embryonal RMS (ERMS) by histopathology.
- To determine whether immunohistochemistry (IHC) assessment for protein expression driven by the fusion protein is an accurate surrogate for fusion status.
- To determine whether FDG PET- CT response assessment following induction chemotherapy is a prognostic biomarker for local failure and/ or survival.

Secondary Objectives (CT3)

- To determine the tolerability of the regimens
- To evaluate the anti-tumour activity and effect on overall survival of VI$_R$R when compared to standard therapy.
- To evaluate the effect on quality of life of VI$_R$R when compared to standard therapy.
- To evaluate the acceptability and palatability of regorafenib formulations
  To examine the pharmacokinetics of regorafenib

Outcome Measures

Randomisation		Outcome measures * primary outcome measure
Phase 1b		RP2D, MTD, Toxicity, DLT, R
Newly diagnosed chemotherapy	Very high risk ($CT1^A$)	EFS*, OS, Toxicity, R
	High risk ($CT1^B$)	EFS*, OS, Toxicity, R
	Maintenance (CT2)	EFS*, OS, Toxicity
Radiotherapy	$RT1^A$ & $RT1^B$	LFFS*, EFS, OS, Acute wound post-operative complications, Acute post-radiotherapy complications, late complications, LRFFS, HRQoL ($RT1^A$ only)
	$RT1^C$	LFFS*, EFS, OS, Acute post-radiotherapy complications, LRFFS, Late complications
	RT2	EFS*, OS, Acute post-radiotherapy complications, LRFFS, HRQoL.
Relapse	CT3	EFS*, OS, Toxicity, BR+, Duration of response+, Duration of BR, OR+, HRQoL, acceptability/palatability, PK, PD, biomarkers
All patients		EFS, OS from the appropriate reference time point(s)
PET sub-study		PET response, EFS, OS and LFFS

Key

BR	Best Response
DLT	Dose Limiting Toxicity
EFS	Event Free Survival
LFFS	Local failure free survival
LRFFS	Loco-regional failure-free survival
HRQoL	Health Related Quality of Life
MTD	Maximum Tolerated Dose
OS	Overall Survival
OR	Objective Response
PD	Pharamcodynamics
PK	Pharmacokinetics
R	Response
RP2D	Recommended Phase II Dose

+ Radiological assessment in relapsed patients

Patient Population

Patients with newly diagnosed and/or relapsed RMS.

Sample Size

- Frontline: A minimum of 840 patients with newly diagnosed RMS
- Relapse: A minimum 260 patients with relapsed/recurrent RMS

Eligibility Criteria

Inclusion Criteria for study entry – Mandatory at first point of study entry

1. Histologically confirmed diagnosis of RMS (except pleomorphic RMS)
2. Written informed consent from the patient and/or the parent/legal guardian

Eligibility Criteria for specific trial questions

See Table 3: Risk Group Assignment for further information on assigning patients to the correct risk group.

Phase 1b Dose Finding - I_RIVA (recruitment complete)

Inclusion

1. Entered in to the FaR-RMS study at diagnosis
2. VHR disease
3. Age >12 months and ≤25 years
4. No prior treatment for RMS other than surgery
5. Medically fit to receive treatment
6. Adequate hepatic function:
    a. Total bilirubin ≤ 1.5 times upper limit of normal (ULN) for age, unless the patient is known to have Gilbert's syndrome
    b. ALT or AST < 2.5 X ULN for age
7. Absolute neutrophil count ≥1.0x 10^9/L
8. Platelets ≥ 80 x 10^9/L
9. Adequate renal function: estimated or measured creatinine clearance ≥60 ml/min/1.73 m^2
10. Documented negative pregnancy test for female patients of childbearing potential

Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active

11. Written informed consent from the patient and/or the parent/legal guardian

Exclusion

1. Weight <10kg
2. Active > grade 2 diarrhoea
3. Prior allo- or autologous Stem Cell Transplant
4. Uncontrolled inter-current illness or active infection
5. Pre-existing medical condition precluding treatment
6. Urinary outflow obstruction that cannot be relieved prior to starting treatment
7. Active inflammation of the urinary bladder (cystitis)
8. Known hypersensitivity to any of the treatments or excipients
9. Second malignancy
10. Pregnant or breastfeeding women

Frontline chemotherapy randomisation VHR - CT1[A]

Inclusion

1. Entered in to the FaR-RMS study at diagnosis
2. VHR disease
3. Age ≥ 6 months
4. Available for randomisation ≤60 days after diagnostic biopsy/surgery
5. No prior treatment for RMS other than surgery
6. Medically fit to receive treatment
7. Adequate hepatic function :

a. Total bilirubin ≤ 1.5 times upper limit of normal (ULN) for age, unless the patient is known to have Gilbert's syndrome
8. Absolute neutrophil count ≥1.0x 10^9/L (except in patients with documented bone marrow disease)
9. Platelets ≥ 80 x 10^9/L (except in patients with documented bone marrow disease)
10. Fractional Shortening ≥ 28%
11. Documented negative pregnancy test for female patients of childbearing potential
12. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active
13. Written informed consent from the patient and/or the parent/legal guardian

Exclusion

1. Active > grade 2 diarrhoea
2. Prior allo- or autologous Stem Cell Transplant
3. Uncontrolled inter-current illness or active infection
4. Pre-existing medical condition precluding treatment
5. Urinary outflow obstruction that cannot be relieved prior to starting treatment
6. Active inflammation of the urinary bladder (cystitis)
7. Known hypersensitivity to any of the treatments or excipients
8. Second malignancy
9. Pregnant or breastfeeding women

Frontline chemotherapy randomisation HR - CT1^B

Inclusion

1. Entered in to the FaR-RMS study at diagnosis
2. HR disease
3. Age ≥ 6 months
4. Available for randomisation ≤60 days after diagnostic biopsy/surgery
5. No prior treatment for RMS other than surgery
6. Medically fit to receive treatment
7. Adequate hepatic function :
    a. Total bilirubin ≤ 1.5 times upper limit of normal (ULN) for age, except if the patient is known to have Gilbert's syndrome
8. Absolute neutrophil count ≥1.0x 10^9/L
9. Platelets ≥ 80 x 10^9/L
10. Documented negative pregnancy test for female patients of childbearing potential
11. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active
12. Written informed consent from the patient and/or the parent/legal guardian

Exclusion

1. Active > grade 2 diarrhoea
2. Prior allo- or autologous Stem Cell Transplant
3. Uncontrolled inter-current illness or active infection
4. Pre-existing medical condition precluding treatment
5. Urinary outflow obstruction that cannot be relieved prior to starting treatment
6. Active inflammation of the urinary bladder (cystitis)
7. Known hypersensitivity to any of the treatments or excipients
8. Second malignancy
9. Pregnant or breastfeeding women

Frontline Radiotherapy

See section 16.2 for further details.

Note: eligible patients may enter multiple radiotherapy randomisations.

Radiotherapy Inclusion – for all radiotherapy randomisations

1. Entered in to the FaR-RMS study (at diagnosis or prior to radiotherapy randomisation)
2. VHR, HR and SR disease
3. ≥ 2 years of age
4. Receiving frontline induction treatment as part of the FaR-RMS trial or with an IVA/IVADo based chemotherapy regimen.. Note that, patients for whom ifosfamide has been replaced with cyclophosphamide will be eligible
5. Patient assessed as medically fit to receive the radiotherapy
6. Documented negative pregnancy test for female patients of childbearing potential
7. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active
8. Written informed consent from the patient and/or the parent/legal guardian

Radiotherapy Exclusion – for all radiotherapy randomisations

1. Prior allo- or autologous Stem Cell Transplant
2. Second malignancy
3. Pregnant or breastfeeding women
4. Receiving radiotherapy as brachytherapy

RT1^{A} Specific Inclusion

1. Primary tumour deemed resectable (predicted R0/ R1 resection feasible) after 3 cycles of induction chemotherapy [1] (6 cycles for metastatic disease)
2. Adjuvant radiotherapy required in addition to delayed surgical resection of the primary tumour (local decision)
3. Available for randomisation after cycle 3 and prior to the start of cycle 5 of induction chemotherapy for localised disease, or after cycle 6 and prior to the start of cycle 8 for metastatic disease

RT1^{B} Specific Inclusion

1. Primary tumour deemed resectable (predicted R0/R1 resection) after 3 cycles of induction chemotherapy[1] (6 cycles for metastatic disease).
2. Adjuvant radiotherapy required in addition to surgical resection (local decision)
3. Higher Local Failure Risk (HLFR) based on presence of either of the following criteria:
    a. Unfavourable site*
    b. Age ≥ 18yrs
4. Available for randomisation after cycle 3 and prior to the start of cycle 6 of induction chemotherapy for localised disease, or after cycle 6 and prior to the start of cycle 9 for metastatic disease

RT1^{C} Specific Inclusion

1. Primary radiotherapy indicated (local decision)

[1] *In special cases where additional chemotherapy may facilitate complex surgical resection, clinicians may continue with 1-3 extra courses before taking the decision concerning local therapy,* ***however in general this is discouraged.***

2. Higher Local Failure Risk (HLFR) based on either of the following criteria:
    a. Unfavourable site*
    b. Age ≥ 18yrs
3. Available for randomisation after cycle 3 and prior to the start of cycle 6 of induction chemotherapy for localised disease, or after cycle 6 and prior to the start of cycle 9 for metastatic disease

*Favourable sites are: GU including bladder-prostate, head & neck non-para meningeal, orbit and biliary primaries.

Unfavourable sites are: All other sites. See Appendix 18: DEFINITION OF SITES and APPENDIX 19 Regional lymph node definition

RT2

1. Available for randomisation after cycle 6 and before the start of cycle 9 of induction chemotherapy.
2. Unfavourable metastatic disease, defined as Modified Oberlin Prognostic Score 2-4**

***Note: Definition of metastatic lesions for RT2 eligibility**

Modified Oberlin Prognostic Score (1 point for each adverse factor):

- Age ≥10y
- Extremity, Other, Unidentified Primary Site
- Bone and/ or Bone Marrow involvement
- ≥3 metastatic sites

Unfavourable metastatic disease: 2- 4 adverse factors

Favourable metastatic disease: 0-1 adverse factors

Maintenance chemotherapy (VHR) - CT2[A]

Inclusion

Randomisation must take place during the 12th cycle of maintenance chemotherapy.

1. Entered in to the FaR-RMS study (at diagnosis or at any subsequent time point)
2. VHR disease
3. Received frontline induction chemotherapy as part of the FaR-RMS trial or with a IVA/IVADo based chemotherapy regimen
    a. Patients for whom ifosfamide has been replaced with cyclophosphamide will be eligible
4. Completed 11 cycles of VnC maintenance treatment (either oral or IV regimens)
5. No evidence of progressive disease
6. Absence of severe vincristine neuropathy – i.e. requiring discontinuation of vincristine treatment)
7. Medically fit to continue to receive treatment
8. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active
9. Written informed consent from the patient and/or the parent/legal guardian

Exclusion

1. Prior allo- or autologous Stem Cell Transplant
2. Uncontrolled intercurrent illness or active infection
3. Urinary outflow obstruction that cannot be relieved prior to starting treatment
4. Active inflammation of the urinary bladder (cystitis)
5. Second malignancy
6. Pregnant or breastfeeding women

Maintenance chemotherapy (HR) - CT2^{B}

Randomisation must take place during the 6th cycle of maintenance chemotherapy.

Inclusion

1. Entered in to the FaR-RMS study (at diagnosis or at any subsequent time point)
2. HR disease
3. Received frontline induction chemotherapy as part of the FaR-RMS trial or with a IVA based chemotherapy regimen. Note that patients for whom ifosfamide has been replaced with cyclophosphamide will be eligible
4. Completed 5 cycles of VnC maintenance treatment
5. No evidence of progressive disease
6. Absence of severe vincristine neuropathy i.e. requiring discontinuation of vincristine treatment
7. Medically fit to continue to receive treatment
8. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active
9. Written informed consent from the patient and/or the parent/legal guardian

Exclusion

1. Prior allo- or autologous Stem Cell Transplant
2. Uncontrolled inter current illness or active infection
3. Urinary outflow obstruction that cannot be relieved prior to starting treatment
4. Active inflammation of the urinary bladder (cystitis)
5. Second malignancy
6. Pregnant or breastfeeding women

Relapse randomisation CT3: VI_RR compared to VI_RT:

Inclusion

1. Entered in to the FaR-RMS study (at diagnosis or at any subsequent time point including at relapse)
2. First or subsequent relapse of histologically verified RMS
3. Age ≥ 6 months
4. Measurable or evaluable disease
5. No cytotoxic chemotherapy or other investigational medicinal product (IMP) within previous three weeks: within two weeks for vinorelbine and cyclophosphamide maintenance chemotherapy
6. Medically fit to receive trial treatment
7. Documented negative pregnancy test for female patients of childbearing potential within 7 days of planned randomisation
8. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active
9. Written informed consent from the patient and/or the parent/legal guardian

Exclusion

1. Progression during frontline therapy without previous response (=Refractory to first line treatment)
2. Prior -regorafenib or temozolomide
3. Active > grade 1 diarrhoea
4. ALT or AST >3.0 x upper limit normal (ULN)
5. Bilirubin, Total >1.5 x ULN; total bilirubin is allowed up to 3 x ULN if Gilbert's syndrome is documented
6. Patients with unstable angina or new onset angina (within 3 months of planned date of randomisation), recent myocardial infarction (within 6 months of randomisation) and those with cardiac failure New York Heart Association (NYHA) Classification 2 or higher
   Cardiac abnormalities such as congestive heart failure (Modified Ross Heart Failure Classification for Children = class 2) and cardiac arrhythmias requiring antiarrhythmic therapy (beta blockers or digoxin are permitted)
7. Uncontrolled hypertension $\geq$ 95th centile for age and gender
8. Prior allo- or autologous Stem Cell Transplant
9. Uncontrolled inter current illness or active infection
10. Pre-existing medical condition precluding treatment
11. Known hypersensitivity to any of the treatments or excipients
12. Second malignancy
13. Pregnant or breastfeeding women

Trial Duration

Anticipated 7 years of recruitment.

Patients will have follow-up assessments for a minimum of 3 years following study entry. Patients will be followed up for progression and death until the end of trial definition has been met.

For CT3: Patients will be followed up for a minimum of 6 years from trial entry (or 5 years from end of relapsed trial treatment, whichever comes later). Patients will be followed up for progression and death until the end of trial definition has been met.

TRIAL SCHEMA

Figure 1: Overall Trial Schema

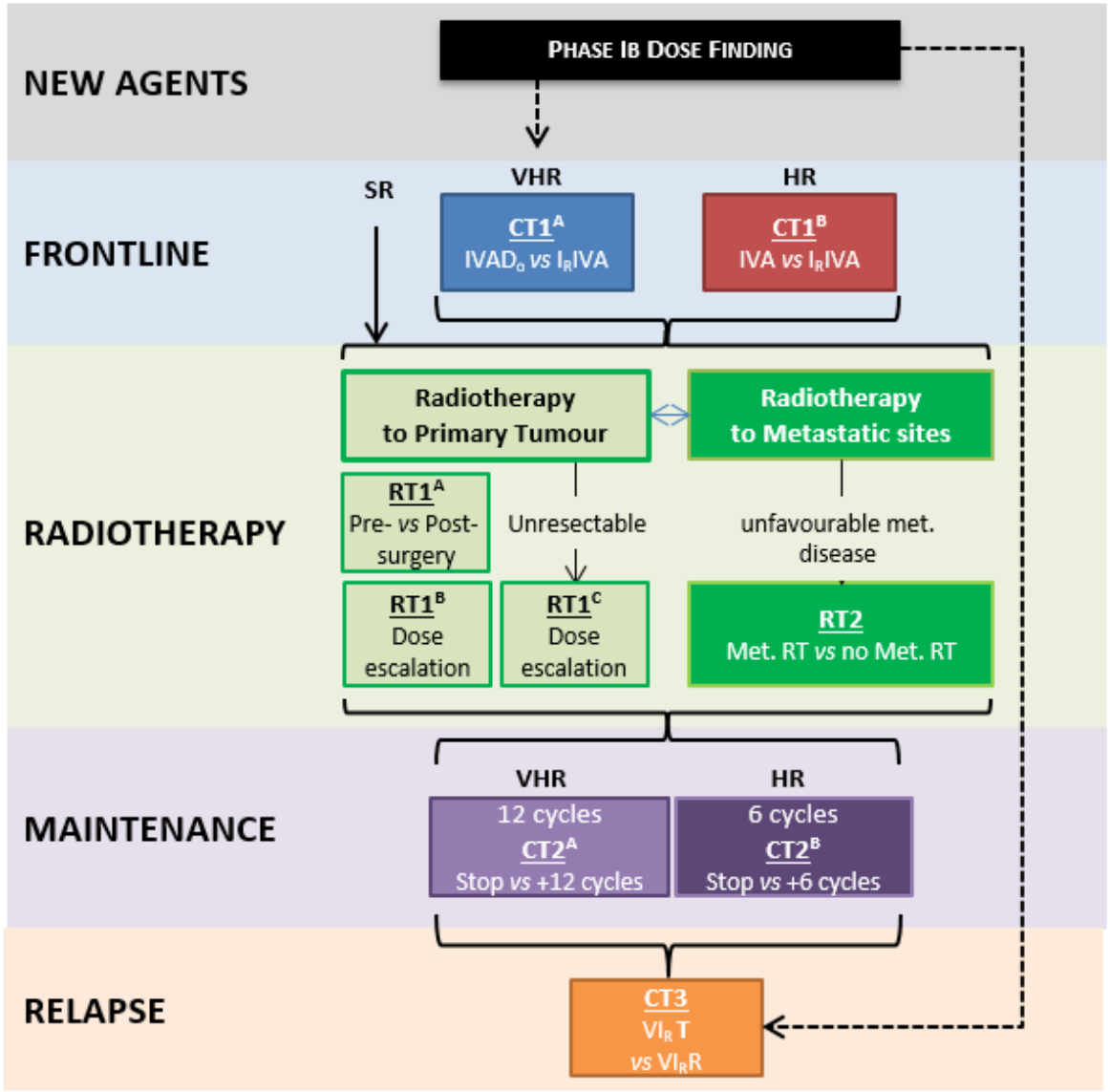


Figure 2: Frontline & Maintenance Trial Schema

+ additional arms can be added to the MAMS design, including safe combinations identified in the FaR-RMS Phase Ib dose finding study. A maximum of three new arms will be added to each of the frontline (VHR and HR) and relapse randomisations; and a maximum of four new arms to the Phase 1b component.

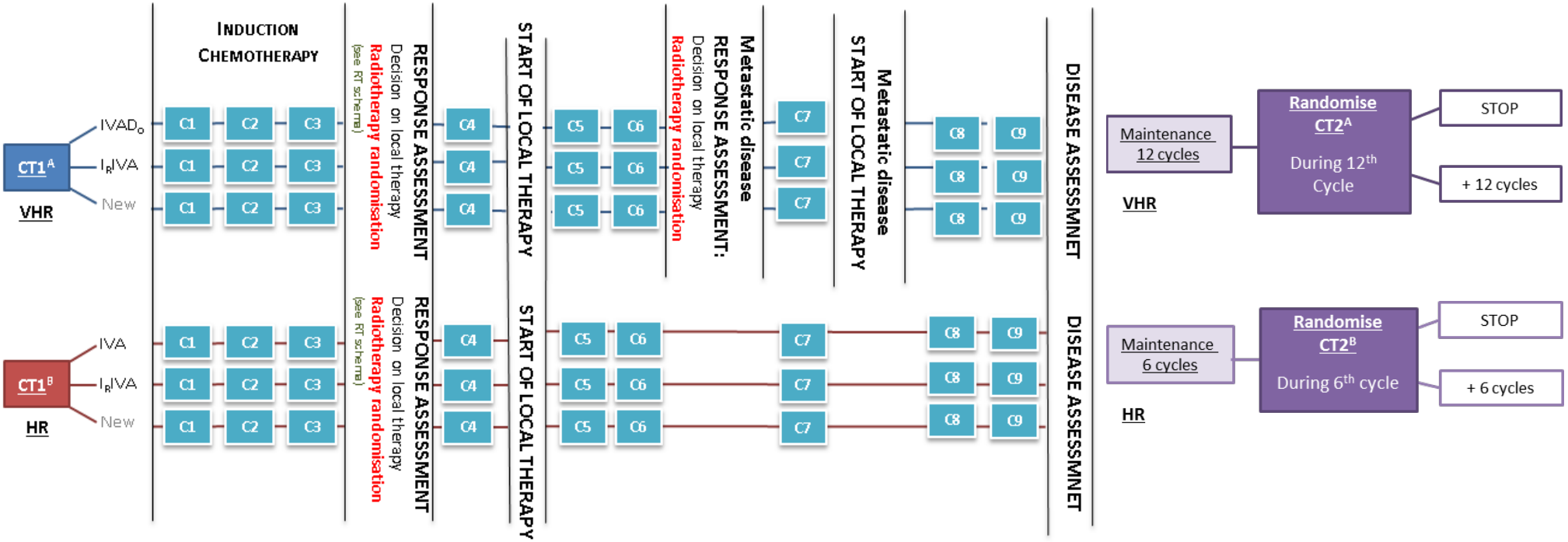
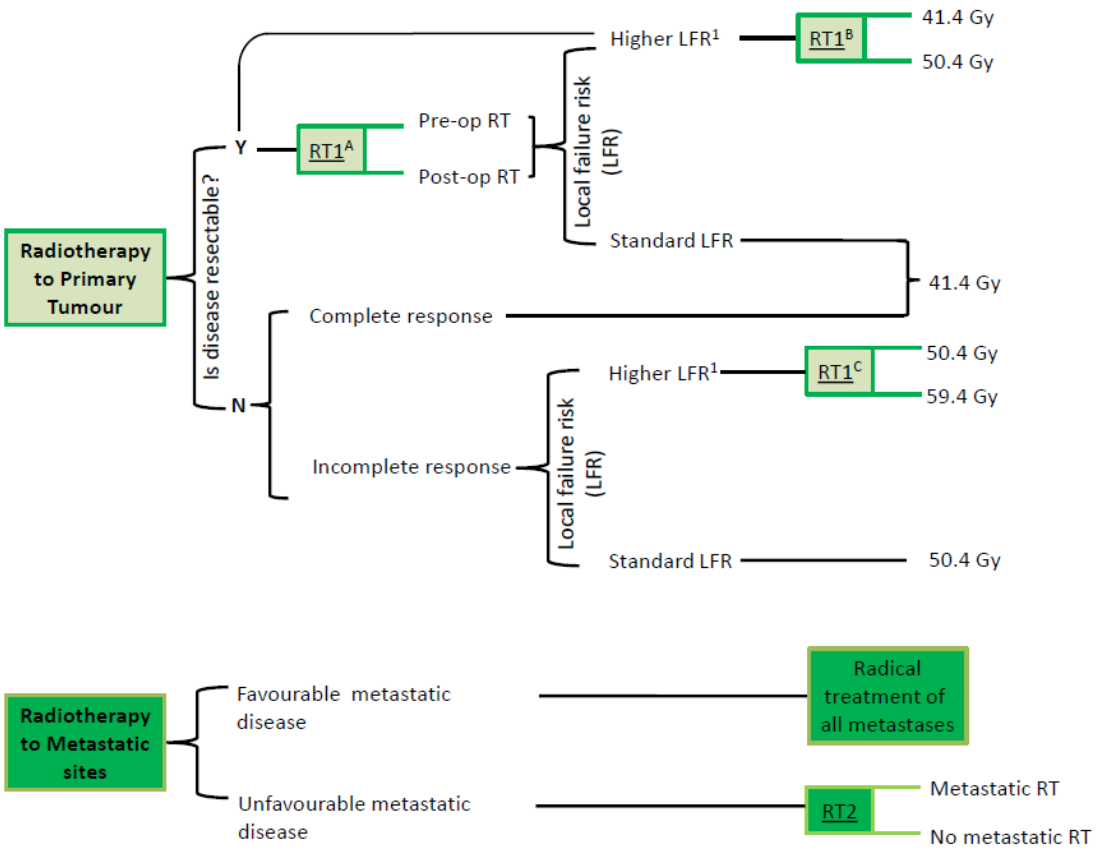


Figure 3: Radiotherapy Trial Schema



1. **Higher LFR:** Unfavourable site* &/ or age ≥ 18yr

***Favourable sites are: GU including bladder-prostate, head & neck non-parameningeal, orbit and biliary primaries .**

Unfavourable sites are: all other sites.

2. **Favourable metastatic disease**: Modified Oberlin Prognostic Score of ≤1
3. **Unfavourable metastatic disease:** Modified Oberlin Prognostic Score of ≥2

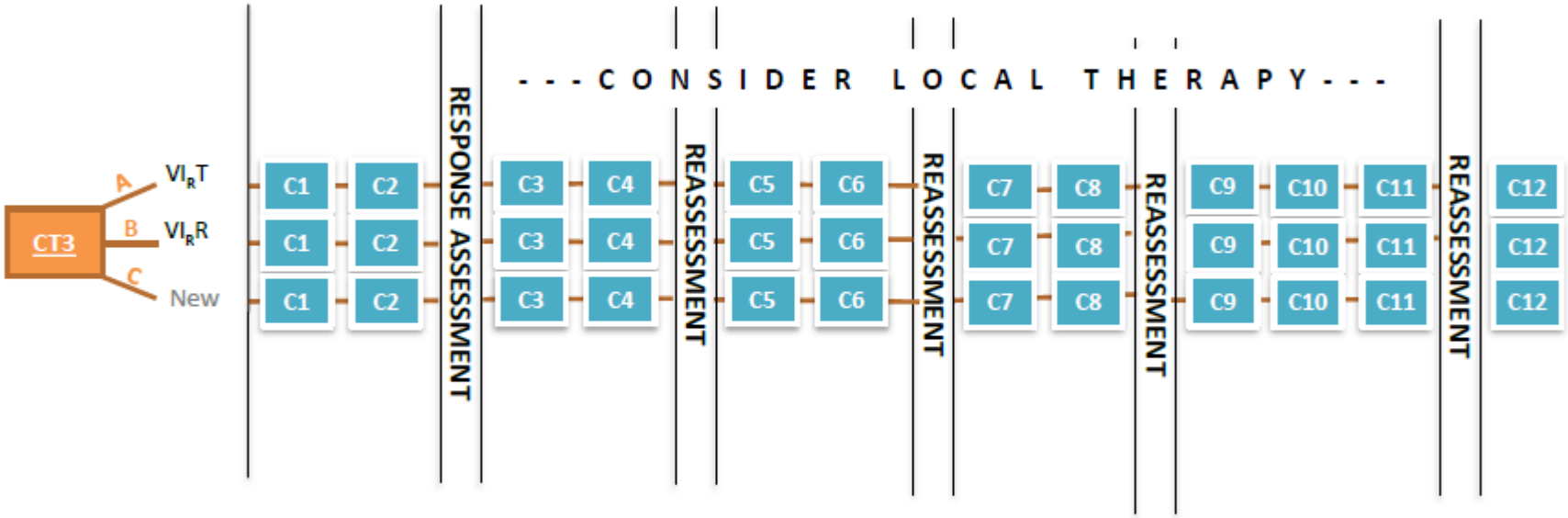
Modified Oberlin Prognostic Score (1 point for each adverse factor):

- Age ≥10y
- Extremity, Other, Unidentified Primary Site
- Bone and/ or Bone Marrow involvement
- ≥3 metastatic sites

See Appendix 18: DEFINITION OF SITES and APPENDIX 19 Regional lymph node definition

Figure 4: Relapse Trial Schema

+ additional arms can be added to the MAMS design, including Phase Ib dose finding



ABBREVIATIONS

ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
AR	Adverse Reaction
ARMS	Alveolar RMS
ALP	Alkaline Phosphatase
ALT	Alanine Transferase
AST	Aspartate Aminotransferase
ANC	Absolute Neutrophil Count
BED	Biological Effective Dose
BM	Bone Marrow
BSA	Body Surface Areas
CCrea	Creatinine Clearance
CI	Chief Investigator
CMFT	Central Manchester University Hospitals NHS Foundation Trust
COG	Childrens' Oncology Group
CR	Complete Remission
CRCTU	Cancer Research UK Clinical Trials Unit
CRF	Case Report Form
CSG	Clinical Study Group
CT	Computerised Tomography
CTV	Clinical Target Volumes
CTRad	Clinical and Translational Radiotherapy (Research Working Group)
CTCAE	Common Terminology Criteria for Adverse Events
CWS	Cooperative Weichteil Sarcoma group
DICOM	Digital Imaging and Communications in Medicine
DFS	Disease Free Survival
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
Do	Doxorubicin
DSUR	Development Safety Update Report
EANM	European Association of Nuclear Medicine
EFS	Event-Free Survival
EORTC	European Organisation for the Research and Treatment of Cancer
EOT	End of Treatment
EpSSG	European paediatric Soft tissue sarcoma Study Group
ERMS	Embryonal RMS
EVCTM	EudraVigilance Clinical Trial Module
EWS	Ewing sarcoma
FDG-PET	Fluorodeoxyglucose-PET

FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescent in situ hybridization
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular Filtration Rate
GP	General Practitioner
GTV	Gross Tumour Volume
GU	Genitourinary
HDT	High-Dose Therapy
HFRT	Hyperfractionated RT
HLFR	High Local Failure Risk
HR	High Risk (disease)
HRQoL	Health Related Quality of Life
HTA	Human Tissue Act
ICF	Informed Consent Form
ICR	Individual Case Review
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
I_R	Irinotecan
I_RIVA	Irinotecan, Ifosfamide, vincristine, actinomycin D
IMI2	Innovative Medicines Initiative 2
IMP	Investigational Medicinal Product
IRS	Intergroup Rhabdomyosarcoma Study
ISF	Investigator Site File
ITCC	(European) Innovative Therapies for Cancer in Children
ITT	Intention-to-treat
ITV	Internal Target Volume
i.v	Intravenous
IVA	Ifosfamide, vincristine, actinomycin D
IVADo	Ifosfamide, vincristine, actinomycin D, doxorubicin
LF	Local Failure
LFFS	Local failure free survival
LRFFS	Loco-regional failure-free survival
MAMS	Multi-arm Multi-Stage
MDT	Multi-Disciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
MMT	Malignant Mesenchymal Tumour
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCC	National Coordinating Centre
NCRI	National Cancer Research Institute
NIMP	Non-Investigational Medicinal Product

OAR	Organ at Risk
OR	Objective Response
OS	Overall Survival
ORR	Objective Response Rate
PD	Pharmacodynamics
PDGFRA	Platelet-derived growth factor receptor A
PERCIST	PET Response Criteria In Solid Tumours
PET	Positron Emission Tomography
PI	Principal Investigator
PIS	Patient Information Sheet
PK	Pharmacokinetics
PR	Partial Remission
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient Reported Outcomes
PROMS	Patient Reported Outcome Measures
PTV	Planning Target Volume
QoL	Quality of Life
QUARTET	Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials
eRDE/eRDC	(electronic) Remote Data Entry/(electronic) Remote Data Capture
R	Response
R&D	Research & Development
REC	Research Ethics Committee
RMS	Rhabdomyosarcoma
RP2D	Recommended Phase II Dose
RR	Response Rate
RT	Radiotherapy
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RTQA	Radiotherapy Quality Assurance
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBRT	Stereotactic Ablative Body Radiotherapy
SF	Shortening Fraction
SIOP	International Society of Paediatric Oncology
SLFR	Standard Local Failure Risk
SPAEN	Sarcoma Patients Euronet
SmPC	Summary Product Characteristics
SR	Standard Risk
SRT	Stereotactic Radiotherapy
STS	Soft Tissue Sarcoma
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBC	To be confirmed
TMG	Trial Management Group

T	Temozolomide
TmP	Tubular Maximum Reabsorption of Phosphate
TNO	Trial Number
TSC	Trial Steering Committee
TSH	Thyroid stimulating hormone
TYA	Teenagers and Young Adults
UICC	Union Internationale Contre le Cancer
UK	United Kingdom
ULN	Upper Limit Normal
USS	Ultrasound Scan
VAC	Vincristine, actnomycin D, cyclophosphamide
VEGF	Vascular Endothelial Growth Factor
VnC	Vinorelbine, cyclophosphamide
VHR	Very High Risk (disease)
VI_RR	Vincristine, irinotecan, regorafenib
VI_RT	Vincristine, irinotecan, temozolomide
Vn	Vinorelbine
VOD	Veno-Occlusive Disease
WMA	World Medical Association

1. BACKGROUND AND RATIONALE

1.1 Background

Rhabdomyosarcoma (RMS) is a rare sarcoma, with 59% of cases presenting in children and the rest occurring in adulthood, where the prognosis is poorer [1, 2]. Although relatively rare, RMS is the commonest of the paediatric soft tissue sarcomas, affecting about 40 children (0-14 years) and 50 teenagers/adults per year in the UK [1]; this excludes pleomorphic RMS which primarily occurs in older adults and is regarded as a different entity with a different clinical behaviour and therapeutic approach [3]. RMS arises in many different sites within the body and comprises two major histological sub-groups: alveolar (ARMS) and embryonal (ERMS) [4]. Because of its chemo-responsiveness, neoadjuvant chemotherapy is used in the majority of patients with a response rate (RR) of around 80-85% [5-7]. However, despite its chemo-sensitivity, multimodality treatment including radiotherapy or surgery or both radiotherapy and surgery is needed to achieve long term local control and cure in the vast majority of cases. This was demonstrated in the Intergroup RMS Study (IRS)-IV study where 695/883 patients with intermediate risk RMS required radiotherapy as part of primary treatment [8]. Patients with metastatic disease can achieve remission with intensive chemotherapy and local therapy in 75% of cases but the vast majority relapse, often at distant sites, resulting in a 3 year event-free survival (EFS) of only 27% [9, 10]. Unfortunately, at the time of relapse, RMS is generally very refractory to treatment and has a 5 year overall survival (OS) of less than 20% [11].

In adults, 20% of patients (8% of total RMS cases) have pleomorphic histology and 80% have histological diagnoses comparable to RMS in children, with predominance of alveolar histology [2]. To date, no clinical trials in adult RMS have been performed; however, a retrospective single centre experience reported that treatment according to paediatric regimens may improve outcome [1]. We therefore have not specified an upper age limit for the FaR-RMS study, only fitness to receive the medical treatment, with the aim of evaluating whether the trial's objectives lead to improved outcomes for RMS across the age spectrum.

Currently, treatment for newly diagnosed patients in the paediatric population is stratified according to age, tumour size, histology (favourable or unfavourable), Intergroup Rhabdomyosarcoma Study (IRS) post-surgical stage and lymph node involvement. This treatment stratification strategy was adopted in the most recent European paediatric Soft tissue sarcoma Study Group (EpSSG) RMS-2005 trial for non-metastatic RMS in children and recent analysis confirms it effectively discriminates survival by subgroup (oral presentation GL De Salvo, EpSSG Winter meeting, Brussels, 2016). Based on recent studies, the FaR-RMS trial will incorporate and investigate use of fusion gene status versus histopathological subtyping in the stratification criteria [12-14].

Currently, three large international groups are conducting randomised clinical trials in paediatric RMS: EpSSG in Europe, the Children's Oncology Group (COG) in North America and Cooperative Weichteil Sarcoma (CWS) group in Germany. The EpSSG RMS 2005 trial for newly diagnosed patients has already demonstrated that the addition of doxorubicin to standard IVA (ifosfamide, vincristine, actinomycin D) chemotherapy does not improve survival in High Risk (HR) RMS [15] and has investigated whether prolonging treatment with 6 months of maintenance chemotherapy (daily cyclophosphamide with weekly vinorelbine) improves survival in HR disease. The RMS 2005 study confirmed that there is a role for maintenance treatment after standard therapy in patients in complete clinical remission (CR). [15, 16]. The primary endpoint of the trial (disease-free survival, measured as time from date of second randomisation up to relapse or death) did not result in a statistically significant difference between the two arms (p=0.06). However, overall survival (OS), a secondary endpoint of the trial, was significantly improved in the maintenance arm. Most of the patients were able to complete their treatment as planned in the protocol and toxicity was acceptable.

The on-going COG intermediate risk RMS trial (similar to EpSSG HR category) is evaluating whether the addition of temsirolimus to standard backbone (vincristine, actinomycin D, cyclophosphamide, VAC) chemotherapy improves survival [ClinicalTrials.gov Identifier: NCT02567435].

In the relapse setting, the recently completed EpSSG randomised phase II trial (VIT-0910; ClinicalTrials.gov Identifier: NCT01355445) evaluated the benefit of adding temozolomide to standard salvage backbone treatment of vincristine and irinotecan (VI_RT) with a primary end point of objective response (OR). VI_RT is now standard therapy in Europe for patients at relapse.

1.2 Trial Rationale

The FaR-RMS trial is a comprehensive clinical research programme that will address both local and systemic therapy questions, incorporating our knowledge of the biology of RMS.

It will address the following objectives:

1. Can outcomes be improved by utilising new combinations of systemic anti-cancer therapies, including the addition of new biologically targeted drugs in:

    i) Frontline treatment for newly diagnosed patients?
    ii) Patients with relapsed disease?

2. Can outcomes be improved though optimising radiotherapy schedules? Three radiotherapy questions will be addressed:

    i) The benefits of delivering adjuvant radiotherapy preoperatively instead of postoperatively. Can dose escalation of radiotherapy improve local control in patients at a higher risk of local failure?
    ii) Can radiotherapy to all metastatic sites in unfavourable metastatic disease reduce the risk of relapse and improve EFS?

3. Can prolongation of maintenance therapy reduce the risk of relapse and improve OS?

4. To validate whether PAX-FOXO1 fusion status be utilised instead of histological diagnosis to improve treatment stratification

5. Can FDG PET-CT response assessment following induction chemotherapy be used as a prognostic biomarker for local control and/ or survival?

1.3 Can outcomes be improved by incorporating, new agents, including biologically targeted drugs, to systemic therapy regimens?

Chemotherapy is an integral component of multi-modality therapy for RMS. In newly diagnosed paediatric patients, multi-agent chemotherapy regimens are currently assigned according to clinical risk factors (Table 3: Risk Group Assignment). The drugs used are combinations of long established cytotoxic agents including alkylating agents, vincristine and actinomycin D. Incremental improvements in outcome have been achieved over the last three decades within clinical trials that have investigated stepwise modifications in the intensity and combinations of these drugs. In low and SR disease, this has proved very successful, with a current 3 year EFS rates of 95% and 77% respectively (personal communication GL de Salvo [17-19]). However, the greatest treatment challenges are in HR, VHR and metastatic disease, as well as at relapse, where progress with currently available agents has been inadequate; EFS remains below 70%, 45%, and 30% respectively and novel approaches are needed [9, 20, 21].

1.3.1 Frontline treatment for newly diagnosed patients

For HR localised RMS, no induction chemotherapy combination has yet proved superior in efficacy to ifosfamide, vincristine and actinomycin D (IVA) in Europe, [7],[20] or vincristine and actinomycin D and cyclophosphamide (VAC) in North America, [18, 22] [23, 24] and although the toxicity profiles differ, no

difference in outcomes was observed between VAC and IVA when these were directly compared [18]. The current standard chemotherapy regimen for HR patients within EpSSG and across Europe is IVA.

For ARMS with involved loco-regional lymph nodes (Group H in the risk stratification within RMS 2005), which accounts for up to 10% of all RMS, an analysis of previous European co-operative studies suggested very poor survival (5 year EFS 39%), and was comparable to that of metastatic disease. Outcomes appeared to have improved in a more recent study (SIOP MMT95: 3-year EFS 57%) [7] and in EpSSG RMS 2005, where patients with alveolar, node positive disease received intensified initial chemotherapy (IVADo: ifosfamide, vincristine, actinomycin D, doxorubicin) and additional 6 months of maintenance chemotherapy with systematic local treatment to primary and nodal sites. With a median follow-up of 64.9 months (range 19.8-116.3) 5-year EFS was 50% (95%CI 39-59)[25]. However, these studies included patients with fusion negative ARMS which is now known to confer a better prognosis (see below). In a recent analysis of patients treated within RMS 2005 study, 5-year EFS in fusion positive, node positive patients was 43% (95%CI 30-56), compared with 74% (54-87) in fusion negative (p=0.01) patients, showing the need for improved treatments for patients with fusion positive disease with lymph node involvement [26].

Metastatic RMS has a dismal prognosis with 3-year EFS of 27% and OS of 34% [9]. Treatment regimens have comprised combinations of IVA or VAC, with other agents with evidence of activity in RMS (for example anthracyclines), given in a window setting, but a good response early in treatment has not resulted in a subsequent survival benefit. The current EpSSG recommendation for induction chemotherapy for metastatic RMS is IVADo x 4 courses followed by IVA x 5 courses, based on the observed activity of single agent doxorubicin in metastatic RMS [27]. A recently completed pharma-sponsored EpSSG/ITCC study investigated the addition of the VEGF-targeted antibody bevacizumab to standard IVADo/IVA in newly diagnosed metastatic soft tissue sarcoma in children (BERNIE study). Unfortunately, bevacizumab did not show a significant improvement in EFS in either the whole group or the RMS subgroup [28]. Although there was no evidence of benefit for the addition of doxorubicin in the EpSSG RMS 2005 study for patients with localized disease, this has not been formally investigated in patients with alveolar, node positive and metastatic disease. Given the very poor survival for these patients, there is a reluctance to reduce therapy further (with the omission of doxorubicin) and IVADo is therefore continued as the comparator arm for fusion positive, node positive and metastatic disease.

In view of the similarly poor outcomes for fusion positive/node positive RMS and metastatic RMS, these groups will be combined in FAR-RMS to give a newly defined VHR group.

1.3.2 Relapsed disease

Outcomes following relapse of rhabdomyosarcoma (RMS) are poor with fewer than 20% of patients salvaged [11] and better therapies are urgently needed. Outcomes are affected by a number of clinical factors including prior treatment [28]. The ability to deliver further local therapy (surgery/radiotherapy) is likely to be a critical factor in localised relapse.

The current European strategy for treatment of relapsed RMS is based on data from the COG group comparing two schedules of vincristine and irinotecan (VI_R) in patients with first relapse of RMS in a randomised phase II trial [21]. Irinotecan was given either as 20 mg/m^2/d intravenously on Days 1-5 and 8-12, with vincristine 1.5 mg/m^2 intravenously on Day 1 and 8 of a 21 day cycle or as 50 mg/m^2/d intravenously on Days 1-5 vincristine on Days 1 and 8. There was no significant difference in response rates (26% vs 37% respectively) nor was there a difference in toxicity, so the shorter schedule was taken forward by the COG group and is now used in front line treatment for all but low risk patients.

Within the EpSSG network, irinotecan has not been used in first line treatment prior to the FaR-RMS study and the 5-day VI_R schedule formed the basis of a recently completed randomised phase II trial, VIT-0910, in relapsed and refractory RMS [29]. This trial evaluated the benefit of adding temozolomide to the standard salvage treatment of vincristine 1.5 mg/m^2 on Days 1 and 8 with irinotecan 50 mg/m^2 on Days 1-5 (VI_RT) with a primary end point of objective response (OR). One hundred and twenty patients were enrolled (60 in each arm). The VI_RT arm achieved significantly better PFS (adjusted

Hazard Ratio (HR)=0.65, 95%CI, 0.43-0.97, p=0.036) and OS (HR=0.53, 95%CI, 0.33-0.83, p=0.005) compared to VI. PFS and OS results were similar when only relapsed patients were included. VI_RT is now standard therapy in Europe for patients at relapse who have already received alkylating agents in first line treatment,and will form the control arm in the relapse randomisations within the FaR-RMS study.

The FaR-RMS relapse study has been designed as an efficient multiarm, multistage trial that allows assessment of new agents that are promising based on emerging biological and pre-clinical data to be combined with VI_RT, VI_R or in other new combinations and tested against a standard treatment arm of VI_RT in patients with relapsed RMS. Regorafenib will be the first targeted agent to be included within the FaR-RMS relapse study.

1.4 Incorporating New Agents into systemic therapy regimens

To try to improve systemic therapy in the frontline setting for HR and VHR (the latter including fusion positive, node positive and metastatic disease) and at relapse, the FAR-RMS trial will investigate the safety and efficacy of new systemic therapy combinations. New therapeutic agents will be introduced for evaluation in FaR-RMS based on sound mechanistic biological and/or empirical evidence as well as availability and prior clinical evidence from other settings and evidence of safety in phase 1 trials.

The first new combination to be investigated in FaR-RMS builds on the promising activity of VI_R described above. We will evaluate irinotecan with IVA (I_RIVA) in the front-line setting. In addition, VI_RR will be examined in a randomised comparison with VI_RT for efficacy in the relapse setting.

Eligible patients will be entered into a Phase Ib component from limited centres with recognised expertise in undertaking paediatric oncology phase I studies. These centres are part of the well-established European network; the Innovative Therapies for Children with Cancer (ITCC) consortium.

The Phase Ib trial designs are based on the Skolnik rolling 6 design (other trial designs may be considered if deemed more appropriate) and will be undertaken in patients with relapsed or refractory disease and/or frontline patients with VHR disease depending on the existing safety and preliminary activity data for the new agent combination. All of these are patients with an extremely high risk of treatment failure and therefore may potentially benefit from the addition of new therapies to standard backbone chemotherapy or new treatment regimens. The decision to investigate in VHR frontline patients or at relapse will depend on the degree of benefit anticipated from the existing preclinical/phase I/II data. A higher anticipated benefit is required for new combinations in VHR frontline patients). The safety and tolerability in combination with standard chemotherapy, i.e. either IVA (frontline) or VI_RT (relapse) will also be taken into account where applicable.

Where the clinical activity of the new treatment regimen is unknown or requires further investigation before adding in to a randomised setting, a single arm expansion, Phase II, cohort to obtain an assessment of activity, will follow-on from the determination of the RP2D. The expansion cohort will be designed on an arm by arm basis.

1.4.1 Irinotecan

Although not a ‘novel’ drug, the topoisomerase inhibitor irinotecan has not been fully evaluated in the frontline setting. Irinotecan is an active agent in RMS and in combination with vincristine, high response rates (70%) were reported in window studies in newly diagnosed metastatic RMS [30]. In adult solid tumours it has been investigated extensively as part of combined modality therapy, including in combination with radiotherapy, as preclinical studies have indicated it to be a radiosensitiser [31].

When standard VAC treatment was compared with VAC alternating with VI_R in intermediate risk RMS, the VI_R combination both showed the same 2-year EFS of 65%, , but the VI_R regimen had reduced haematological toxicity and reduced risk of gonadotoxicity from reduced cumulative cyclophosphamide dose [32].

Recently published results of the COG ARST0431 study [33] reported improved survival (compared to historical reports) for patients with metastatic RMS who received dose intensification by interval compression, in patients with more favourable disease i.e. one or fewer risk factors identified previously [9]; these patients had a 3-year EFS of 67% compared with 44% in among similar patients in previous studies. For patients with 2 or more risk factors, 3 year EFS remained unchanged; 20% versus 14% EFS [9].

In FaR-RMS, standard 3-weekly IVA, given in week 1 of each course will be intensified by adding 5 days of Irinotecan in week 2 (I_RIVA); the result is dose intense chemotherapy throughout weeks 1 and 2. Irinotecan causes relatively mild bone marrow suppression and, therefore, should be suitable for this dose intense combination with IVA chemotherapy [34].

The benefit of irinotecan **in a dose-intense combination** with frontline induction chemotherapy will be explored in the HR and the newly defined VHR groups**.** It is proposed to establish the recommended phase II dose (RP2D) of irinotecan in combination with IVA (I_RIVA) in a Phase Ib setting for VHR patients before the efficacy evaluation of this dose-intense regimen is extended to include both VHR and HR groups. In the VHR group I_RIVA will be tested against the IVADo and in the HR group I_RIVA will be compared to IVA (control arm).

For irinotecan in **relapsed disease see 1.3.2**

1.4.2 Doxorubicin

Doxorubicin is an effective drug in the treatment of RMS. However, its role as part of a multi-drug regimen for patients with VHR disease remains controversial. An IRS phase II window in children with newly diagnosed metastatic rhabdomyosarcoma demonstrated the efficacy of ifosfamide and doxorubicin with a 63% CR+PR rate at 12 weeks [35]. Furthermore, the preliminary results of a window study with doxorubicin in HR RMS (65% CR+PR) supported the value of doxorubicin as an active drug in RMS[27]. However, in the recent EpSSG RMS 2005 study in patients with localised disease no benefit was identified when doxorubicin was combined with IVA chemotherapy. In a series of randomised trials performed by the IRS Group, no difference in survival and progression-free survival for patients with RMS treated with VAC or VAC plus anthracyclines was identified. In IRS-I, the addition of 5 courses of vincristine, doxorubicin and cyclophosphamide to VAC did not improve the result [36]. In IRS-II, a similar comparison, but with higher cumulative doses of Doxorubicin (480 mg/m2) showed no improvement [37]. In IRS III, a further randomised comparison did not yield different results. However, it was noted that a more complex therapy including administration of doxorubicin and cisplatin appeared to result in significant improvement for some subgroups of patient: IRS group I/II alveolar histology and special pelvic sites [23]. Survival outcomes for patients with VHR disease remain poor, so in spite of a lack of robust evidence for benefit, there remains a reluctance within the clinical setting to remove doxorubicin from treatment for these patients.

1.4.3 Regorafenib

Regorafenib: preclinical studies in RMS

Regorafenib is a potent, oral multi-kinase inhibitor that targets a broad range of angiogenic, stromal and oncogenic kinases, including vascular endothelial growth factor receptors (VEFGR) 1, 2 and 3, tyrosine kinase with immunoglobulin and epidermal growth factor homology domain 2 (TIE2), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptors (FGFR), c-KIT, RET, RAF-1 and BRAF (wild-type and V600E mutant). It is approved for the treatment of adult patients with metastatic colorectal cancer, gastrointestinal stromal tumours (GIST) and hepatocellular carcinoma. The antitumor activity of regorafenib is thought to be mediated primarily by its antiangiogenic properties and accompanied by proapoptotic activity.

In vitro studies have shown regorafenib causes a moderate growth inhibition of RMS cell lines and a significant tumour growth delay *in vivo* in all tumour models [38]. No partial or complete remissions were observed as single agent, except for the IGRM57 medulloblastoma model, which is PDGFRA amplified, suggesting that the PDGF signalling pathway may be involved in the therapeutic effect of regorafenib. PDGFRs are potential targets for RMS treatment with several biologic activities linking to PDGF

signalling in RMS [39]. Furthermore, PDGFRA has been identified as a transcriptional target of the PAX3-FOXO1 fusion protein, and using a mouse model for PAX3-FOXO1 fusion positive RMS, temporary growth inhibition of 8-14 days was demonstrated *in vitro* and *in vivo* by targeting PDGFRA [40]. In preclinical models complete regression was observed when regorafenib was combined with DNA damaging agents such as irinotecan or radiotherapy in PDGFRA gene amplified tumors but not in non-amplified ones [38]. FGFR1 and 4 may also be important targets in RMS [41-45].

Regorafenib: clinical studies in RMS

The paediatric phase I Study 15906 (REGOPEDS) of regorafenib in paediatric subjects with solid malignant tumors that were recurrent or refractory to standard therapy [46] demonstrated one transient partial remission and one disease stabilisation among the 3 RMS patients enrolled. The recommended phase 2 dose (RP2D) was defined as 82 mg/m^2 q.d. in a 3-weeks-on/1 week-off schedule. Toxicity was consistent with adverse event (AE) profile seen in adults, apart from a higher incidence of grades 3/4 hematological toxicities in heavily pretreated patients (prior history of myelosuppressive therapies such as high dose chemotherapy with stem cell rescue or craniospinal irradiation). Regorafenib exposure in children was in a similar range to that observed in adults and a high between-subject variability was observed, with no apparent correlation of exposure by age.

To explore the potential to develop regorafenib in combination with chemotherapy, the REGOPEDS study was amended to test an escalating dose of regorafenib in combination with VI$_R$ chemotherapy [47]. Patients 6 months to 18 years old with relapsed/refractory RMS or a solid malignant tumor for which VI$_R$ was considered an adequate treatment at relapse (Ewing sarcoma, hepatoblastoma, neuroblastoma and Wilms tumor) were included and at least 50% of patients were required to have RMS. Prior treatment with vincristine and/or irinotecan was allowed. Two different dosing schedules were tested owing to concerns about an increase in the AUC of irinotecan and SN-38 when given following regorafenib dosing (Cycle 2) in metastatic colorectal cancer: Vincristine 1.5 mg/m^2 (Days 1 and 8) and irinotecan 50 mg/m^2 (Days 1-5) were combined with daily oral regorafenib either on Days 1-14 (concomitant schedule) or on Days 8-21 (sequential schedule) in a 21 day cycle. Patients aged 2-18 years received regorafenib 72 mg/m^2 escalating to 82 mg/m^2; patients 6-24 months 60 mg/m^2 escalating to 65 mg/m^2.

Twenty-one patients including 12 RMS, 5 Ewing sarcoma, 3 neuroblastoma and 1 Wilms tumour were treated overall, 2 in the concomitant schedule and 19 in the sequential schedule. Concomitant dosing was discontinued when several grade 3 dose-limiting toxicities were reported in both patients (peripheral neuropathy and liver injury; pain, vomiting, febrile aplasia). Toxicities observed were among those expected with no new types of toxicities reported although greater incidence of grade 3-4 haematologic toxicities was seen with the combination. The most common grade ≥3 treatment-emergent AEs were neutropenia (71%), thrombocytopenia (33%), leukopenia (29%), anaemia (24%), and an increased ALT (24%). Irinotecan had to be reduced in 62% of the patients due to toxicity. The maximum tolerated dose and recommended phase 2 dose of regorafenib in the sequential schedule was 82 mg/m^2.

Radiological responses were observed in 7 of 12 patients with RMS (1CR, 6PR). Responses were seen in patients with both embryonal and alveolar histology and also in patients who previously received irinotecan chemotherapy. Two patients remain on treatment for more than 1 year. Overall, the VI$_R$R regimen has shown reassuring preliminary activity in a relapsed/ refractory RMS patient population. Safety and toxicity signals in the VI$_R$R combination indicate that the toxicity level is in the range of the VI$_R$T combination and it is not expected that a combination of VI$_R$R with temozolomide would be tolerated. The level of activity seen for the VI$_R$R combination was considered sufficient and worth proceeding to the randomized phase 2 stage against standard VI$_R$T chemotherapy during a Bayer advisory board in October 2019 with international pediatric sarcoma experts.

Clinical pharmacology of regorafenib

Regorafenib will be available as both tablet and granulate formulation. The tablet and granulate formulations of regorafenib given under fasting conditions, were comparable with respect to C_{max} and

Area Under the Curve (AUC) of regorafenib. The 90% confidence intervals for the geometric least squares (LS) mean ratios of the exposure were calculated to be 0.91 to 1.14 (C_{max}) and 0.967 to 1.09 (AUC) and were fully within the bioequivilence limits (0.8 to 1.25). Therefore, it can be considered that the granulate formulation of regorafenib exhibis bioavailability that is comparable to the comericially available 40mg tablet formulation which has been used in pivotal clinical trials.

The PK of metabobolite M-2 and M-5 were also nearly bioequivalent for both formulations. AUC and C_{max} of the tablets and granulate (fasted) were bioequivalent with respect to M-2 whereas AUC (0-t_{last}) and Cmax for M-5 were slightly lower with the granulate formulation. This may be attributed to the high variability observed for M-5.

1.4.4 Other agents

Evidence for additional agents will be taken from the literature and/or preclinical biological studies from EpSSG-linked and other laboratories, including investigations coordinated through the EpSSG Biology Committee. EpSSG members are also involved in other European initiatives including Innovative Medicines Initiative 2 (IMI2) and ITCC that will facilitate preclinical and clinical investigations. These include generation and testing of patient derived xenografts, access to drugs, as well as biomarker identification and validation. National molecular profiling initiatives for relapsed tumour samples have or are being established and will be linked to FaR-RMS. In addition, computational and bioinformatics analyses of profiling data will be used to identify potential molecular vulnerabilities for preclinical testing. These activities are expected to lead to clinical testing of further novel agents within FaR-RMS.

1.5 Can outcomes be improved by novel radiotherapy schedules?

Despite the significant improvements in outcomes for patients in the last 20 years, local control remains the principal challenge in localised RMS. Radiotherapy is a key component of local therapy for RMS and analyses from the SIOP (International Society of Paediatric Oncology) MMT (Malignant Mesenchymal Tumour) 84, 89 and 95 trials in paediatric RMS [48] supported the more systematic use of radiotherapy that was adopted in the current EpSSG RMS 2005 trial. In EpSSG RMS 2005, 86% of patients with localised HR-RMS received radiotherapy, with the trial reporting an increase in 3-year EFS from 55% to 67% for HR patients and from 39% to 56% for node positive alveolar patients [20, 25], yet local failure was still observed in the majority of relapse cases. It is proposed that the effectiveness of radiotherapy in local control could be improved by modifying the dose and/or the timing of radiotherapy. Within FaR-RMS both strategies will be investigated.

1.5.1 Radiotherapy Dose Escalation

The current strategy for radiotherapy has been established over the last 40 years in European and US collaborative group studies. Doses ranging from 36 to 55Gy (conventionally fractionated) and 59.4Gy (hyperfractionated radiotherapy: HFRT) have been employed. In the SIOP MMT studies, 45Gy was the recommended dose, plus 5Gy for microscopic residual or 10Gy for macroscopic residual disease [48]. The true impact of dose escalation for RMS patients where there is a higher local failure risk has not been adequately investigated. To date, only the COG IRS IV study has asked a randomised radiotherapy question comparing HFRT (59.4Gy in 54 x 1.1Gy twice daily fractions) with 50.4Gy conventional fractionation (1.8Gy once daily). This study showed no difference in local control suggesting that the biological effective dose (BED) for tumour control with 59Gy, when delivered in this hyperfractionated schedule (using a low dose per fraction) was similar to 50.4Gy delivered using conventional fractionation, and in fact there had not been true radiotherapy dose escalation [49]. Increased acute toxicities were observed in the HFRT arm, and therefore conventional fractionation remains the gold standard for RMS.

The potential benefits of radiotherapy dose escalation in RMS still need to be determined. In the IRS II- IV studies [50], patients with macroscopic disease after first surgery received <47.5Gy radiotherapy; a higher rate of local failure of 35% was observed for tumours ≥5cm size compared to 18% for tumours <5cm. Yet patients who received > 47.5Gy had a lower rate of local failure of 15%, irrespective of tumour

size. Size ≥ 5cm was also identified as a key factor increasing the risk of local failure in the COG D9803 study. COG is also proposing the dose escalation to 59.4Gy with conventional fractionation for all RMS patients with a higher local failure risk that they are defining as tumour size at diagnosis ≥ 5cm; however, the effects of this dose escalation are not being investigated within a randomised setting. An unpublished multivariate analysis from the RMS 2005 study, IRS Group 3 patients with localised disease up to the age of 21 years (personal communication Gian Luca Di Salvo) has shown only unfavourable site, to be associated with a higher local failure risk (HLFR); size >5cm was not an independent risk factor for local failure. As both the acute and late toxicities of radiotherapy are known to increase when higher doses of radiotherapy are used, it is important to identify those at higher HLFR where the benefits of improved tumour control potentially resulting from radiotherapy dose escalation are more likely to outweigh the potential consequences.

Adult patients are known to have worse outcome, including local failure, but to date have been excluded from the majority of collaborative group RMS studies. Therefore, FaR-RMS will ask the question whether radiotherapy dose escalation can improve local control for RMS patients with a HLFR, including those with an unfavourable primary site and those aged 18 years or older.

1.5.2 Timing of Radiotherapy

Historically radiotherapy for RMS has been delivered after surgical resection. However, preoperative radiotherapy has a number of potential advantages over postoperative radiotherapy: the accuracy in defining the radiotherapy field is improved because the intact tumour target volume is easier to define; the residual tumour may act as a form of 'spacer', meaning that less uninvolved normal tissue is exposed to the higher radiotherapy dose; a significant proportion of the irradiated tissue will be removed surgically, which may reduce the risk of second tumours; there is a biological rationale as the tumour and surrounding tissues are less hypoxic than in the postoperative setting and hypoxia increases tumour radio-resistance [51]. In soft tissue sarcoma (STS), preoperative radiotherapy has been increasingly used in standard clinical settings. O'Sullivan [52] showed a small significant improvement in OS in adult patients with extremity STS randomised to receive preoperative radiotherapy at 50Gy instead of postoperative radiotherapy at 66Gy, although this was counterbalanced by an increased risk of acute wound complications. Preoperative radiotherapy is being investigated in a number of non-rhabdomyosarcoma STS studies, including NCT01344018 and NCT02180867. There is limited published experience on preoperative radiotherapy for RMS: a cohort of 17 patients with bladder-prostate RMS in the German CWS96 study had a reported a 5-year EFS of 82% [53]. In the current EpSSG RMS 2005 trial, preoperative radiotherapy was an option available to the treating radiation oncologist, but its effects have not been systematically evaluated. In the FaR-RMS trial, the efficacy (local control), safety and impact on Health Related Quality of Life (HRQoL) of preoperative radiotherapy in RMS compared to standard postoperative radiotherapy will be investigated.

1.5.3 Radiotherapy to metastatic sites

There are conflicting data as to whether radiotherapy to metastatic sites truly influences outcomes for RMS. To date, the standard of care for metastatic RMS has been systematic irradiation of all metastatic sites whenever feasible (MTS-2008 registry study for metastatic RMS within RMS 2005 [28]), in sharp contrast to guidelines for adult soft tissue sarcomas where radiotherapy to metastatic sites is not standard of care. In the COG studies patients with >3 metastatic sites are categorised as having extensive metastatic disease and radiotherapy is delivered at week 20. Radiotherapy for these patients is challenging and COG advise that certain metastatic sites are prioritised, leaving other sites where radiotherapy may need to be omitted or delivered later at week 47. However, these guidelines have been open to interpretation and unpublished data from the EpSSG MTS 2008 study (personal comm. GL De Salvo) have shown, of 129 patients where radiotherapy data were available, only 16% received radiotherapy to the primary and all sites of metastatic disease, 73% did not receive radiotherapy to all sites of disease and 56% had no radiotherapy to metastatic sites. Similarly in the recent randomised BERNIE study, evaluating bevacizumab in combination with standard chemotherapy, showed that of 102 metastatic RMS patients only 31 had radiotherapy to all sites, 49 had radiotherapy to some sites (partial radiotherapy) and 22 had no radiotherapy; OS was improved in those receiving radiotherapy although selection bias could have contributed to this [54] . A small single centre series of 13 patients

with metastatic RMS or Ewing sarcoma (EWS) receiving systematic radiotherapy (>40Gy) to all metastatic sites reported a local control rate for metastases of 92% and OS of 35%, both at 5 years [55]. A further series of six patients with metastatic RMS, treating all metastases with radiotherapy (41.4Gy- 50.4Gy), achieved 100% local control, yet out of field relapses were seen in 50% and median OS was only 31.8 months[56].

For patients with lung metastases only (approximately 28% of patients), the evidence of a benefit for whole lung radiotherapy is also mixed. A retrospective analysis of 46 patients from the IRS IV study revealed that 25 received whole lung radiotherapy and 16 did not, with the treatment strategy determined by the treating centre with no randomisation; those receiving lung radiotherapy had fewer lung recurrences, but the difference in OS (47% vs 31%) was not significant [57]. A report from CWS on 29 patients with ERMS and lung only metastases showed a complete response to induction chemotherapy in 22. [58]. Ten patients received local therapy (9 whole lung radiotherapy and 3 metastatectomy); however, 19 patients did not, without any apparent effect on OS, EFS or the rate of local relapse in the lungs.

Apart from the lack of clear evidence that radiotherapy to all sites including metastases is effective, it can have an adverse impact on HRQoL in a patient group with a dismal prognosis and can produce myelosuppression limiting the delivery of further chemotherapy. A multivariate pooled analysis from US and European cooperative groups, published in 2008, has defined the following prognostic factors for RMS patients with metastatic disease[9]:

- Age <1y or ≥10y
- 'Unfavourable' site: Extremity, Other, Unidentified
- Bone or Bone Marrow involvement
- ≥3 metastatic sites

In this analysis there was a clear separation in EFS between groups; patients with ≤1 risk factor having a favourable 3 year EFS of 44%, whereas those with ≥2 prognostic factors having a more unfavourable outcome with a 3 year EFS of only 14%. FaR-RMS aims to investigate whether radiotherapy to metastatic sites improves survival for patients with unfavourable metastatic RMS and evaluate the effects on HRQoL of this treatment.

1.6 Can prolongation of maintenance therapy reduce the risk of relapse and improve overall survival?

Patients with RMS respond well to initial chemotherapy and CR or nearly complete PR can be achieved with multimodality therapy. The challenge in the HR patient categories is to maintain disease remission by eliminating minimal residual disease. Since more than 90% of events in localized RMS appear > 12 months after diagnosis, i.e. off-therapy, new approaches with longer low-dose treatments, so-called maintenance or metronomic chemotherapy, have been developed. Besides proven anti-angiogenic activity, other potential mechanisms of action have been proposed, such as restoration of anti-cancer immune response and induction of tumour dormancy [59, 60]. Two phase II studies in relapsed/refractory RMS patients combined weekly intravenous vinorelbine with continuous daily oral cyclophosphamide (VnC) resulting in response rate rates of 36 and 37% [61, 62]. In a previous CWS group study, the efficacy of high dose therapy (HDT) versus a 6-month oral maintenance treatment was evaluated in patients with metastatic soft tissue sarcoma (n=74 RMS) [63]. After a median follow-up of 57.4 months, OS for the whole RMS group was 39% (maintenance group: 52%, HDT group 27%, p= 0.03). However, the assignment of treatment in this study was by physicians' decision. In a recent multivariate analysis, as part of a pooled analysis in RMS of the extremities, longer treatment duration was positively associated with survival [64]. Additionally, in the recent COG experience, reduction of cyclophosphamide dose (total cumulative cyclophosphamide dose of 4.8 g/m^2) has been associated with an increased risk of recurrence in a subset of low risk RMS [65].

In the EpSSG-RMS-2005 trial, HR patients in clinical complete remission at the end of standard induction treatment were randomised between stopping therapy or 6 months prolongation with maintenance therapy combining weekly 25mg/m^2 intravenous vinorelbine with continuous daily 25 mg/ m^2 oral cyclophosphamide (VnC). 371 patients were randomised from 20-4-2006 to 21-12-2016. Preliminary analyses presented at the EpSSG meeting in Lyon, December 2017 (Gian Luca de Salvo) for 5 year disease-free survival (DFS) (measured as time from date of randomisation to relapse or death) showed a Hazard Ratio of 0.68 (95% CI 0.45-1.02), p-value of 0.06 in favour of maintenance

treatment. For OS, Hazard Ratio was 0.52 ((95%CI 0.32-0.86); p-value: 0.01) in favour of maintenance therapy. So, although analysis of the primary endpoint of the trial (DFS) did not result in a statistically significant difference between the two arms, OS, a secondary endpoint, was significantly improved in the maintenance arm. In addition, the median time to an event was 8.9 months (range, 3.9-16.1, and 10.1 months (range, 6.9-15.4) in 'stop treatment' arm and 'maintenance' arm, respectively. The median time to event was longer in the maintenance arm, and the majority of the events occurred after the 6 months of VnC maintenance had been completed. The majority of patients were able to complete their treatment as defined by the protocol and toxicity was acceptable. Further analyses are ongoing; however, these preliminary results support randomisation between continuing maintenance treatment for a further 6 months (12 months total) versus stopping treatment after 6 months of standard maintenance chemotherapy in FaR-RMS with standard maintenance administration comprising weekly intravenous vinorelbine and continuous daily oral cyclophosphamide.

Patients with metastatic disease in the BERNIE Study [28] received 12 months of VnC therapy. The optimal duration of maintenance therapy for patients in the highest risk disease categories will be evaluated in FaR-RMS with a 12 vs 24 months VnC maintenance randomisation for VHR RMS. Because of the length of maintenance duration, oral vinorelbine in addition to oral cyclophosphamide maintenance may be considered in this patient population. Indeed, oral vinorelbine is widely used in the adult population for malignancies (breast, colorectal, NSCL cancers) but also benign tumors such as fibromatosis and was found to have acceptable and reliable pharmacokinetic profiles at clinically relevant dosage levels. In adults, oral vinorelbine has approximately 40% bioavailability; thus, a dose of 60 mg/m^2 orally is the equivalent of 25 mg/m^2 intravenously [66]. In a previous Phase II study of vinorelbine and continuous low doses cyclophosphamide in children and adolescents with a relapsed or refractory malignant solid tumour, bioequivalence data demonstrated that both Body Surface Area (BSA)-standardized clearance and total drug exposure following 25 mg/m^2 vinorelbine were equivalent between children >4 years and adult series [62]). Conflicting results have been reported in a previous Phase I in paediatric cancer patients by COG with oral (week 1) and iv (weeks 2 to 6) vinorelbine) [67]. Higher mean intravenous total body clearance was observed compared with adult reports and mean oral bioavailability was 28.5 ± 22.5% with the apparent oral clearance and volume of distribution substantially higher than in adults given similar oral doses. Oral vinorelbine was generally well-tolerated in this paediatric population. Because it was not expected that oral vinorelbine will have a different PK profile in children than in adults, an additional study is in progress in low-grade glioma in France (oral vinorelbine in children/adolescents: efficacy and PK analysis, final results December 2018). Importantly, and by contrast to intensive induction chemotherapy, the doses of VnC chemotherapy are adapted according to hematologic toxicity with the goal to avoid grade 3/4 neutropenia and grade 3/4 thrombocytopaenia. Haematologic toxicity reflects individual variability but also previous therapy during induction including radiation therapy on bone (on primary tumor but also in FaR-RMS metastatic sites). Thus, despite conflicting results regarding PK analysis in children/adolescents, full oral maintenance including oral low-dose cyclophosphamide and oral vinorelbine will be an option for patients with VHR disease. Oral vinorelbine will provide patient convenience and better patient acceptance in the context of prolonged VnC maintenance. Therefore for the patients receiving 12 months of standard maintenance chemotherapy either the i.v or oral formulation of vinorelbine may be used. For those randomized to 24 months oral vinorelbine will be used. Additionally, for young patients (< 4 years) and patients with difficulty swallowing tablets or capsules the intravenous vinorelbine formulation can be considered. However, for HR RMS patients, vinorelbine will still be given intravenously based on data from EpSSG-RMS-2005 protocol.

1.7 Use of PAX and/or FOXO1 fusion gene in risk stratification

Recent EPSSG and COG clinical trials for RMS have used ARMS and ERMS histological subtype alongside other clinical parameters to allocate patients to a risk group that will determine their treatment intensity [22]. The majority (70-80%) of ARMS cases have translocations resulting in fusion of the *PAX3* or *PAX7* gene with *FOXO1.* Rare variant rearrangements constitute an estimated 1% of all RMS [14]. *PAX-FOXO1* fusion gene positive cases with ERMS histology have also been described in 1% of patients [68]. Previous studies including large-scale gene expression profiling have revealed that ARMS tumours lacking characteristic fusion genes are molecularly and clinically indistinguishable from ERMS [14, 69]. This is consistent with studies that show the fusion genes confer a negative clinical prognostic value [12, 14, 70-72]. Important validation of this came from analysis of outcome by fusion status in prospectively collected samples from intermediate risk patients in the COG D9803 study which showed

that 5-year EFS was poorer for those with tumours that were ARMS *PAX3-FOXO1* fusion positive (54%) and *PAX 7-FOXO1* fusion positive (65%) than those with ERMS (77%; P < 0.001). EFS for fusion negative ARMS (ARMSn) and ERMS did not reach statistical difference (90% vs. 77%, P = 0.15)[13]; In addition, an analysis by fusion status of 33 ARMS cases enrolled in the COG D9602 low risk study also showed a 5yr EFS of 100% for fusion negative and 81% for fusion positive although this did not reach statistical significance. OS was 100% for fusion negative and 85% for fusion positive (CI 51%, 96%, p = 0.27) for fusion negative ARMS [73].

Based on these studies and an increasing understanding of the functional role of the fusion proteins in RMS, this study will use PAX3 or PAX7 and/orFOXO1 fusion gene status rather than histology to stratify patients. This is consistent with the approach that is being utilised by the COG RMS Study Group. We expect 7% of patients to change risk groups and treatment will be reduced for the >25% of patients with alveolar histology tumours that lack these fusion genes [68]. The use of fusion gene status in risk stratification, rather than histological sub-type, is anticipated to stratify treatment more accurately and result in a proportion of patients benefiting from lower treatment associated toxicities. However, it is critical to assess whether outcome is compromised in patients where treatment is reduced.

It is also important to assess the approach to determining the fusion gene status: it is not clear whether it is necessary to assess fusion status in all patients with embryonal histology and certain immunohistochemical markers which are elevated in ARMS [74, 75] may prove to be surrogates for assessing fusion status.

1.8 Prospective validation of value of FDG-PET response as prognostic biomarker to identify those at highest risk for local failure

There is a need to define prognostic biomarkers to identify patients at HLFR. FDG PET-CT is a promising imaging biomarker for predicting response to chemotherapy. In Hodgkin's lymphoma interim FDG PET-CT has shown encouraging results when used as a prognostic tool early in the course of treatment of advanced Hodgkin lymphoma, allowing for a reduction in treatment for patients with favorable characteristics, while suggesting a benefit from changing therapy for those with a positive scan [76].

In paediatric RMS: a single centre study, evaluating PET-CT in RMS at multiple time points [77] reported only 6% local failure (LF) at 3 years (72% 3y PFS) for cases that were FDG negative at week 12 (post induction chemotherapy and prior to local therapy) but 21% LF (44% 3y PFS) for cases that were still FDG avid at week 12 [77]. However, a subsequent report from the COG group of a selection of patients enrolled on two therapeutic trials failed to confirm the predictive value of FDG-PET response [78]. A systematic review of FDG PET CT in RMS has identified the need to further assess FDG-PET CT in paediatric RMS to better evaluate its potential role as prognostic biomarker [79]. We will therefore also address a secondary question to determine the value of FDG PET-CT response after 3 cycles as a predictive biomarker of local failure and/ or survival in rhabdomyosarcoma.

1.9 Benefit Risk Assessment

Please see the following information relating to known and expected benefits and risks associated to the proposed study regime, as well as measures taken in accordance to the risk profile of the medicinal product.

1.9.1 Chemotherapy

All of the IMPs within this trial are either licensed for use in RMS and/or within regimens that have been widely used (within trials and/or as part of standard of care) in this indication in paediatrics, except for regorafenib. The toxicities associated with the IMPs on this trial are well known. However, new combinations or prolonged therapy may give increased risk of toxicity, and not all of the combinations are fully established practice in the adult setting.

This study involves a phase 1b dose finding trial in which irinotecan is added to an established chemotherapy regimen of IVA to create a new regimen, IrIVA. The benefits of adding irinotecan to an IVA regimen have not yet been explored in newly diagnosed patients. The protocol has therefore been

designed to first establish a safe dose of irinotecan in combination with IVA and then if established to take this safe dose forward into Phase II testing of activity. The RP2D of irinotecan in combination with IVA (IrIVA) will be tested in VHR patients before the efficacy evaluation of this dose-intense regimen is extended to additionally include HR risk patients. Although this chemotherapy combination has not been fully explored before in a frontline setting (i.e. in newly diagnosed patients), published data on combining irinotecan and vincristine treatment for RMS showed a positive response.

The frontline randomisations will not open until the phase 1b dose finding study is complete as the recommended phase II dose of IrIVA is required. Once deemed to be safe, IrIVA, will be tested against the current standard of care IVADo) in VHR patients and IVA in HR patients.

The randomisations for maintenance are lower risk: the maintenance randomisations concern additional cycles of the current, well-tolerated standard of care treatment.

The relapse randomisation follows on from the conclusion of the VIT 0910 clinical trial in which temozolomide (T) was added to Vincristine and Irinotecan (VI_R) chemotherapy for relapsed patients. (VI_RT). This is now the standard of care for relapsed patients. The first new arm in the relapse randomisation is exploring whether the addition of regorafenib to vincristine and irinotecan (VI_RR) improves outcomes compared to VI_RT.

As many of the chemotherapy agents are associated with different types of toxicity, all patients must be fit to receive treatment as per the eligibility, and specific stipulations are in place to ensure that patients have sufficiently recovered from haematological, hepatic cardiac and neurological toxicity. Nephrotoxicity will be monitored through regular assessment of Glomerular Filtration rate and cardiac function will be assessed for those on Doxorubicin. Liver function tests will be performed at baseline and prior to each cycle of IMP and further monitoring as per institutional guidelines. Due to the have active diarrhoea greater than CTCAE Grade 2 (grade 1 at relapse). Enhanced monitoring of patients in the relapse question has been introduced due to the still emerging toxicity profile of regorafenib in combination. Dose modifications for toxicity are provided in the protocol.

1.9.2 Radiotherapy

This study will also examine how changes to current radiotherapy standard of care may improve the outcome for patients with RMS. It will examine whether radiotherapy dose escalation can positively affect outcome for those at a higher risk of local failure, as measured by both survival and quality of life. The increase in dose may cause additional toxicity but may result in better clinical results. All patients will be closely monitored during their radiotherapy treatment and toxicities managed according to clinical requirements.

Other patients may receive radiotherapy at an alternative time point to standard of care. The current standard is postoperative radiotherapy. It is hoped that altering the timing of radiotherapy will improve clinical outcomes for patients as well as reducing side-effects. The use of preoperative radiotherapy can increase the short term risk of wound complications and may reduce some long term toxicities. These are endpoints of the study and will be carefully monitored and evaluated.

A further radiotherapy randomisation will look at the risk to benefit ratio of delivering radiotherapy to metastatic sites for those with extensive metastatic disease. There is currently no standard approach to the delivery of radiotherapy to extensive metastatic sites. It could be that increased treatment results in a better clinical outcome but there is also a lack of evidence that radiotherapy to all sites is effective, may be more toxic and may have an adverse impact on QoL It is hoped that the evidence obtained from this randomisation will answer whether the risk: benefit ratio for radiotherapy to patients with extensive metastatic sites is acceptable. Some patients will receive less radiotherapy which may be associated with reduced treatment related toxicity.

All individual per-patient radiotherapy plans for all randomisations will be reviewed by a radiation clinician and medical physics expert within the QUARTET programme prior to commencing radiotherapy to ensure that the plans are in-line with the protocol and safe to deliver. QUARTET is a European wide initiative to improve the quality assurance of radiotherapy delivered to paediatric cancer patients. Such a process will also help standardise the radiotherapy being delivered within the FaR-RMS trial. The radiotherapy will be delivered in accordance with local institutional and or national practice/guidelines, including does modifications for toxicity and for delays.

Radiotherapy is very carefully planned in advance so that the radiation doses which will be received by healthy parts of the body are kept as low as reasonably achievable and within recognised safe limits. For this reason, sometimes the intended tumour dose is limited.

Some patients who are very young may require general anaesthetic to lie still when receiving radiotherapy. However, the use of play specialists often minimizes the need for general anaesthetic.

Radiotherapy carries the following risks of long term side effects however, as radiotherapy is part of the standard treatment pathway for patients with RMS, the risks are similar to those if not treated as part of the FaR-RMS trial:

- developing second cancers
- problems with puberty and fertility (pelvic radiotherapy)
- growth and development problems (cranial/head and neck radiotherapy)
- effects on kidney and liver function
- effects on heart and lung function
- effects on spinal cord function

At all stages of the trial the patients will be carefully monitored for side effects and instructions for dose modifications will be provided. The Data Monitoring Committee (DMC) will meet at regular intervals (more frequently during Phase 1b), and will advise the Trial Steering Committee of any concerns over the relationship between increased/altered treatment in relationship to toxicity and outcome.

1.9.3 Pregnancy and breast feeding

As many of the IMPs in this trial are known to be toxic to the foetus/newborn child, patients of childbearing potential will be required to have a negative pregnancy at the time of trial entry and will have regular pregnancy tests during treatment. Patients should use effective contraception during treatment and for 12 months (6 months for men) afterwards. Female patients should not breast feed whilst receiving these IMPs (ineligible at the point of trial entry).

Adequate contraceptive methods are defined in the protocol and patients will be informed that they must use contraception and discuss this with their doctor prior to starting therapy.

Should a patient or their partner become pregnant the patient will be required to be withdrawn from trials treatment and the pregnancy outcome will be monitored. If a patient's partner becomes pregnant during this period, we would also like to collect details of the outcome of the pregnancy with their permission.

1.9.4 Scans

As part of this study, patients may have x-rays, PET-CT scans and CT scans. These scans use ionizing radiation and therefore are associated with a small risk of secondary cancer. However, the majority of these scans are standard of care.

If a patient takes part in the FDG-PET Substudy they may have one more PET-scan than standard of care.

Young patients may require sedation or a general anaesthetic so they lie still for the scans. General anaesthetic / sedation is generally well tolerated but may result in complications such as allergic reaction or breathing problems.

1.9.5 Collection and use of samples

Patients will have samples taken for histological diagnosis as part of standard of care. These would commonly be standard of care. Formalin fixed paraffin embedded (FFPE) blocks and slides will be collected from each routinely performed biopsy and are an essential part of the FaR-RMS trial for pathology review and assessment of fusion gene status. These are to be sent at diagnosis, second surgery and relapse (where available). Patients will consent for such samples to be used for ethically approved research related to the trial if there is sufficient tissue available. The storage and future use of left over samples is explained in the patient information sheet and consent will be obtained for this. Samples taken as part of this trial will be available for ethically approved research.

Some patients will require lumbar punctures as part of the screening process, although this is part of standard of care. The associated risks are small and include pain, bleeding, bruising and headache. For some patients these investigations will be performed under sedation/general anaesthetic.

1.9.6 COVID-19 pandemic

The risks of the COVID-19 pandemic on the conduct of the study have been assessed and no significant additional risks have been identified. The pandemic has had no impact on the design of the study.

2. OBJECTIVES AND OUTCOME MEASURES

Primary Objectives

Phase I Dose Finding Studies

- To determine the recommended phase II dose (RP2D) of new systemic therapy regimens.
    - The first combination to be tested is irinotecan in combination with ifosfamide, vincristine and actinomycin D (I_RIVA)

Frontline Chemotherapy Questions

- To compare systemic therapy regimens for patients with VHR disease at diagnosis (**CT1^{A}**).
    - The first new combination regimens to be compared are IVADo and I_RIVA in a dose intense schedule
- To compare new systemic therapy regimens with standard chemotherapy for patients with HR disease at diagnosis (**CT1^{B}**). The standard chemotherapy is ifosfamide, vincristine, actinomycin D (IVA) (**CT1^{B}**).
    - The first new combination regime to be compared is irinotecan combined with IVA (I_RIVA) in a dose intense schedule

Radiotherapy Questions

- To determine whether pre-operative or standard post-operative radiotherapy is better for patients with resectable disease (**RT1^{A}**)
- To determine whether dose escalation of radiotherapy improves the outcome in patients with a higher local failure risk (**RT1$^{B/C}$**)
- To determine whether radiotherapy treatment of all sites of disease, including metastatic sites, when compared to radiotherapy treatment to the primary site and involved regional lymph nodes alone, improves the outcome for patients with unfavourable metastatic disease (**RT2**)

Maintenance Chemotherapy Questions

- To determine whether the addition of a further 12 cycles of vinorelbine and cyclophosphamide (VnC) to standard 12 cycles of maintenance chemotherapy (i.e. 24 cycles total) improves the outcome for patients with VHR disease at diagnosis (**CT2^{A}**)
- To determine whether the addition of a further 6 cycles of VnC (intravenous (i.v) vinorelbine, oral cyclophosphamide) to the standard 6 cycles (i.e. 12 cycles total) improves the outcome for patients with localised HR disease at diagnosis (**CT2^{B}**)

Relapsed RMS Question

- To determine whether new systemic therapy regimens improve event-free survival in relapsed RMS compared to standard therapy (VI_RT) (**CT3**):

  Initial new systemic therapy combination to be tested:

- Regorafenib (R) added to vincristine and irinotecan (VI_R) (VI_RR)

Overarching Secondary Objectives

- To validate whether the use of fusion status (PAX3/PAX7-FOXO1) in place of histopathological diagnosis improves risk stratification
- To determine whether assessment of fusion status is necessary in tumours classified as Embryonal RMS (ERMS) by histopathology
- To determine whether immunohistochemistry (IHC) assessment for protein expression driven by the fusion protein is an accurate surrogate for fusion status
- To determine whether FDG PET- CT response assessment following induction chemotherapy is a prognostic biomarker for local failure and/ or survival.

Secondary Objectives (CT3)

- To determine the tolerability of the regimens
- To evaluate the anti-tumour activity and effect on overall survival of VI_RR when compared to standard therapy
- To evaluate the effect on quality of life of VI_RR when compared to standard therapy
- To evaluate the acceptability and palatability of regorafenib formulations
- To examine the pharmacokinetics of regorafenib

Exploratory Objectives (CT3)

- To explore pharmacodynamic effects of the regorafenib combination arm
- To evaluate potential prognostic and/or predictive biomarkers in tumour materials and blood in both regimens
- To evaluate the prognostic and/or predictive potential of diffusion-weighted MRI in both regimens

Definition of Outcome Measures

The trial includes a common set of outcome measures (listed in Table 1: Outcome Measures)

A subset of these will be measured in each randomised group, with a primary outcome measure selected from the common set specifically for each group.

Event-free survival (EFS) time is defined as the time from the reference time point* to first failure event. Failure events are:

- Relapse or progression of existing disease, or occurrence of disease at new sites (clinical or radiological progression per RECIST 1.1) ,
- Death from any cause without disease progression,
- Second malignant neoplasm

Overall survival (OS) time is defined as the time from the reference time point* to death from any cause.

* For each randomisation, the reference time point for EFS and OS is the date of randomisation.

Local failure free survival (LFFS) time is defined as time from randomisation to first local failure event. A local failure event is relapse or progression of tumour at the primary site at any time even if there has been a prior /concurrent, regional or distant failure.

Loco-regional failure-free survival (LRFFS) time is defined as time from randomisation to first local and/or regional failure event. Local failure events are as per LFFS definition. A regional event is relapse or progression of tumour at regional lymph nodes at any time even if there has been a prior distant failure.

For all time-to-event outcome measures, patients who have not experienced a relevant event will be censored at their last follow-up date.

Toxicity will be categorised and graded using Common Terminology Criteria for Adverse Events (CTCAE v 4) (see APPENDIX 9).

Acute wound complications and post-operative complications are defined as specific grade 3 and above within 120 days from surgery according to CTCAE v 4 and Clavien Dindo scale (see APPENDIX 10) [80]. Specific wound complications within the same time frame will also be collected

Acute post-radiotherapy complications are defined as any event grade 3 and above within 120 days from the start of radiotherapy according to CTCAE v 4.

Late local therapy complications are defined as specific grade 3 and above events according to CTCAE and Clavien-Dindo scale occurring after 120 days from start of first local therapy.

Health related quality of life (HRQoL) will be assessed using PedsQL for the paediatric population (under 18 years) and EORTC QLQ-C30 for patients 18 years of age and over.

Response (R) is defined as complete (CR) or partial response (PR) and is clinically defined. Patients who are not assessable for response – e.g. because of early stopping of treatment or death – will be assumed to be non-responders. Response will be assessed after course 3 and 6 for the newly diagnosed chemotherapy very high risk and high risk randomisations.

Objective response (OR) is defined as CR or PR and is defined radiologically per RECIST 1.1. Patients who are not assessable for response – e.g. because of early stopping of treatment or death – will be assumed to be non-responders. OR will be assessed after 2 cycles and at each subsequent protocol-based or clinically indicated assessment.

Duration of response is defined as time from the date of first response (as defined above) to date of first event defined as EFS.

In the relapse question this is defined as time from the date of first objective response (as defined above

Best response (BR) will be assessed throughout the treatment for relapse randomisation.

In the relapse question this will be reported as best of CR, PR, SD, PD or non-evaluable as defined by RECIST 1.1.

Duration of BR: is defined as time from the date of BR (CR, PR, SD) to first event as defined by EFS.

Recommended phase 2 dose (RP2D) is based on tolerability, where tolerability is evaluated through the occurrence of dose limiting toxicity (DLT). DLTs will be defined in the relevant protocol section for each Phase Ib study.

Maximum tolerated dose (MTD) is defined as the dose level at which no or one participant experiences a DLT when at least two of three to six participants experience a DLT at the next highest dose.

PET response will be assessed by PERCIST criteria [81] and visual 'Deauville like' criteria after 3 cycles of chemotherapy. See APPENDIX 11.

Table 1: Outcome Measures

Randomisation		Outcome measures * primary outcome measure
Phase 1b		RP2D, MTD, Toxicity, DLT, R
Newly diagnosed chemotherapy	Very high risk (CT1[A])	EFS*, OS, Toxicity, R
	High risk (CT1[B])	EFS*, OS, Toxicity, R
	Maintenance (CT2)	EFS*, OS, Toxicity

Radiotherapy	RT1[A] & RT1[B]	LFFS*, EFS, OS, Acute wound post-operative complications, Acute post-radiotherapy complications, late complications, LRFFS, HRQoL (RT1[A] only)
	RT1[C]	LFFS*, EFS, OS, Acute post-radiotherapy complications, LRFFS, Late complications
	RT2	EFS*, OS, Acute post-radiotherapy complications, LRFFS, HRQoL.
Relapse	CT3	EFS*, OS, Toxicity, BR[+], Duration of response[+], Duration of BR OR[+], HRQoL, acceptability/palatability, PK, PD, biomarkers
All patients		EFS, OS from the appropriate reference time point(s)
PET sub-study		PET response, EFS, OS and LFFS

Key

BR	Best Response
DLT	Dose Limiting Toxicity
EFS	Event Free Survival
LFFS	Local failure free survival
LRFFS	Loco-regional failure-free survival
HRQoL	Health Related Quality of Life
MTD	Maximum Tolerated Dose
OS	Overall Survival
OR	Objective Response
PD	Pharamcodynamics
PK	Pharmacokinetics
R	Response
RP2D	Recommended Phase II Dose

[+] Radiological assessment in relapsed patients

Recruitment period and follow up:

Recruitment is anticipated to be for 7 years. Patients will be followed up for a minimum of 3 years from trial entry. In CT3 patients will be followed up for a minimum of 6 years from trial entry (or 5 years from end of relapsed trial treatment, whichever comes later). Patients will be followed up for progression and death until the end of trial definition has been met. Recruitment per group is shown below in Table 2: Recruitment per group.

Table 2: Recruitment per group

Randomisation		Minimum Number of patients in total	Assumed baseline event free rate for the primary outcome, 3-year (%)
Radiotherapy	1a	350	80
	1b	315	79
	1c	350	72
	2	210	40
Newly diagnosed chemotherapy	Very high risk	370	35
	High risk	470	65
	Very high risk maintenance	260	35 to 45
	High risk maintenance	240	65
Relapse		260 for the regorafenib question 420 in 7 years with additional arms	30, 1-year

3. TRIAL DESIGN

FaR-RMS is an over-arching study for patients with newly diagnosed and relapsed RMS including multi-arm, multi-stage questions with three principal aims. These are to evaluate:

- systemic therapy through the introduction of new agent regimens in the most advanced disease states: VHR, HR and relapse
- the duration of maintenance therapy
- radiotherapy to improve local control in VHR, HR and (SR) patients and to treat metastatic disease

In addition the study will evaluate:

- risk stratification through the use of PAX-FOXO1 fusion gene status instead of histological subtyping
- the use of FDG PET-CT response assessment as a prognostic biomarker for outcome following induction chemotherapy

3.1 Risk Group Assignment

Patients will be treated according to the risk group assignment in Table 3: Risk Group Assignment. **This risk group assignment has been amended from the previous RMS2005 trial risk group assignment based on analyses performed on outcome data from RMS2005**:

- Fusion status replaces histology as a stratifying factor (GL de Salvo, EpSSG-RMS2005 trial statistician).
- **There is a change in the Risk group stage for certain groups**:
  - Former subgroup D now upstaged to HR
  - GU-bladder/prostate and biliary downgraded to favourable sites
  - The new VHR group includes metastatic disease.

Table 3: Risk Group Assignment

Risk Group	Subgroup	Fusion Status	IRS Group	Site	Node Stage	Size or Age
Low Risk	**A**	Negative	I	Any	N0	Both Favourable
Standard Risk	***B***	Negative	I	Any	N0	One or both Unfavourable
	C	Negative	II, III	Favourable	N0	Any
High Risk	***D***	Negative	II, III	Unfavourable	N0	Any
	E	Negative	II, III	Any	N1	Any
	F	Positive	I, II, III	Any	N0	Any
Very High Risk	***G***	Positive	II, III	Any	N1	Any
	H	Any	IV	Any	Any	Any

Risk Group assignment is determined at diagnosis

Fusion status: Where fusion gene status is unavailable histopathology will be use. Non-alveolar disease should be defined as fusion gene negative and alveolar disease should be defined as fusion gene positive.

Site: Favourable sites are: GU including bladder-prostate, head & neck non-parameningeal, orbit and biliary primaries. Unfavourable sites are: all other sites. See APPENDIX 18 and APPENDIX 19

Node Stage: N0 = 0 positive lymph nodes, N1 = ≥ positive lymph nodes

Age: Favourable is defined as age over 1 and under 10 years of age at diagnosis

Size: Favourable primary tumour is ≤5 cm in longest diameter, patients that are assessed as not evaluable, they will be included in >5cm group)

IRS Group: Please see APPENDIX 16 for further information.

3.1.1 Definition of pulmonary/pleural and peritoneal metastatic disease

The following will be considered as **metastatic pulmonary disease** (assuming there is no other clear medical explanation for these lesions):

- one or more pulmonary nodules of 10 mm or more diameter or;
- two or more well-defined nodules of 5 to 10 mm diameter or;
- 5 or more well-defined nodules smaller than 5 mm;

Hence, 4 or less small nodules (<5mm) at diagnosis will **not** be considered as pulmonary metastatic disease and should be classified only as "**non-specific pulmonary lesions**". Biopsy is NOT recommended.

The same lung window settings should be used when pulmonary nodules are being measured at diagnosis and follow-up.

For patients with pleural effusion or ascites, examination of the fluid is strongly recommended. If malignant cells are found on morphology, the patients will be treated as per the VHR group.

If peritoneal or pleural nodules are evident on imaging, the tumour will be considered as metastatic and treated accordingly.

Where a small amount of fluid is present (e.g. a tumour located below the diaphragm with limited ipsilateral pleural effusion or small volume pelvic fluid collection), this may be “reactive”, and sampling is not necessary.

4. ELIGIBILITY

4.1 Inclusion Criteria

4.1.1 Inclusion Criteria for study entry

Mandatory at first point of study entry

1. Histologically confirmed diagnosis of RMS (except pleomorphic RMS)
2. Written informed consent from the patient and/or the parent/legal guardian

4.1.2 Inclusion Criteria for specific randomisations/registrations:

See relevant sections below

4.2 Exclusion Criteria

4.2.1 Exclusion Criteria for study entry

None

4.2.2 Exclusion Criteria for specific randomisations/registrations

See relevant sections below

4.3 Lifestyle guidelines

Patients with reproductive potential must agree to use an adequate (i.e. with a failure rate of less than 1% per year) method of birth control during the period of therapy.

Men should be advised not to father a child for 6 months after receiving the last dose of study treatment and should use a barrier method of contraception during this time.

Women of childbearing potential should be advised to use effective contraception to avoid pregnancy for 12 months after the last dose of study treatment. Effective contraceptive methods include implants, injectables, combined oral contraceptives, intrauterine device (IUD or coil) and true sexual abstinence* or vasectomised partner.

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Sperm or egg preservation should be offered as per standard practice to patients at risk of irreversible infertility, where appropriate. However, men must refrain from donating sperm for 6 months after receiving the last dose of study treatment.

*Sexual abstinence must be in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the trial, and withdrawal are not acceptable methods of contraception.

5. INFORMED CONSENT

It is the responsibility of the Investigator or person to whom the Investigator delegates the responsibility, to obtain written informed consent for each patient prior to performing any trial-related procedure in compliance with national regulations. Where this responsibility has been delegated, this must be explicitly stated on a Site Signature and Delegation Log (or country specific equivalent).

There are multiple points at which informed consent must be obtained. Consent must be obtained separately at Study Entry and then at each randomisation or registration (Phase 1b) time point. Country specific Patient/Parent Information Sheets (PIS) are provided to facilitate this process.

Investigators must ensure that they adequately explain the aims, trial treatments, anticipated benefits and potential hazards of taking part in the trial to the patient and/or parent/legal guardian as appropriate. The Investigator should also stress that the patient and/or parent/legal guardian is completely free to refuse to take part in or withdraw from the trial at any time. The patient and/or parent/legal guardian should be given sufficient time (e.g. 24 hours) to read the PIS and to discuss the patient's participation with others outside of the site research team if they wish to. The patient and/or parent/legal guardian must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient and/or parent/legal guardian to refuse to participate in the trial without giving a reason must be respected.

As the trial includes both child and adult patients, written consent/assent will be obtained from the patient wherever it is possible to do so (as appropriate according to age and national legislation). There is a section on the parent/legal guardian consent form where assent can be obtained from the patient. For those children who are not able to read, write or understand regarding assent, the clinician will explain the study and obtain verbal assent which will be documented in the patient's medical records. Patients should be re-consented at the age of majority in accordance with national guidance/legislation.

If the patient and/or parent/legal guardian agrees to participate in the trial, they should be asked to sign and date the latest version of the Informed Consent Form (ICF). The Investigator must then sign and date the form on the same day. A copy of the ICF should be given to the patient and/or parent/legal guardian, a copy should be filed in the patient's medical records, and the original placed in the Investigator Site File (ISF) or country specific equivalent. Once the patient is entered into the trial, the patient's trial number should be entered on the ICF that is filed in the ISF. If allowed by country specific legislation/guidance) and if the patient and/or parent/legal guardian has given explicit consent, a copy of the signed ICF must be sent in the post to the applicable National Coordinating Centre (NCC) for review. Where national guidelines do not permit transfer of ICFs outside of the treating organisation, consent will be monitored by the relevant NCC at site visits.

Details of the informed consent discussions should be recorded in the patient's medical records; this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the PIS and ICF. Throughout the trial, the patient and/or parent/legal guardian should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient, in which case the process above should be followed and the patient's right to withdraw from the trial respected.

Electronic copies of the PIS and ICF are available from the applicable NCC and should be printed or photocopied onto the headed paper of the local institution where required by country specific legislation/guidance.

Investigators will be expected to maintain a screening log of all potential study participants. This log will contain limited information about the potential participant and will include the date and outcome of the screening process.

With the patient's or parent/legal guardian's prior consent, the patient's medical practitioner (General Practitioner (GP) in the UK) should also be informed that he or she is taking part in the trial. A GP Letter is provided electronically for this purpose, but it is anticipated that both this letter and the PIS will be translated and adapted in accordance with national practices.

5.1 Screening

Note that assessments conducted as standard of care do not require informed consent. Trial specific investigations must not be undertaken without prior written informed consent.

5.1.1 Screening Assessments Prior to Study Entry

A histologically confirmed diagnosis of RMS is required for Study Entry.

A molecular diagnostic result is not mandatory but every effort should be made to obtain a result prior to Study Entry to ensure that the patient is assigned to the correct risk group (see Table 3).

The local pathologist has an essential role in the FAR-RMS study:

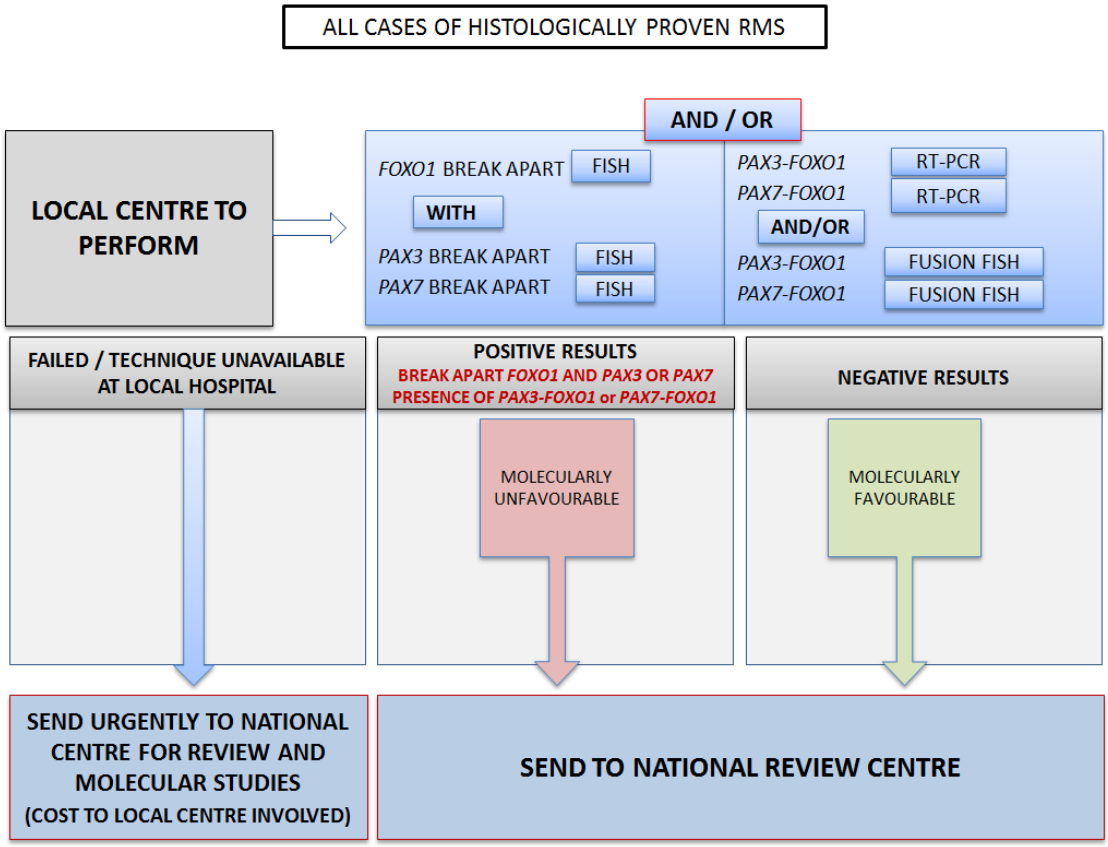
1. The diagnosis and subtyping of RMS is made by the local pathologist.

2. Molecular diagnostics on all cases of RMS should be carried out at the local centre, as the presence of a PAX3-FOXO1 or PAX7-FOXO1 fusion gene is important for patient risk stratification.

3. Where local assessment is not possible or fails, the sample should be sent to the National Pathology Coordinator for an urgent review. The National Pathology Coordinator and EpSSG International Pathology Panel are willing to offer real time review, and the review diagnosis will be communicated directly to the referring pathologist

4. For all patients, a formalin fixed paraffin embedded (FFPE) block together with an pseudo-anonymised Pathology report, if available, and molecular results, if available, should be sent to the National Pathology Coordinator as soon as possible after diagnosis.

More information is provided in the EpSSG Pathology Guidelines and FaR-RMS Laboratory Manual.



6. TRIAL ENTRY

Patients can be entered into the trial once the applicable NCC has confirmed that all regulatory requirements have been met by the trial site and the site has been activated by the UK Coordinating Centre.

To participate in the FaR-RMS trial, the patient and/or patient's parent/guardian will sign the appropriate Study Entry ICF. An ICF will also be required for entry in to each subsequent trial randomisation or registration in to Phase 1b. Patients entering subsequent trial randomisations or registrations will retain the same trial number (TNO). Registration at Study Entry is mandatory. All other trial randomisations and registrations are separate and are not a pre-requisite for future randomisations.

6.1 Procedure for Online Study Entry, Randomisation and Registration

Informed consent must be obtained prior to performing Study Entry and any specific trial randomisation or registration. Study Entry and each randomisation or registration should be performed by sites using the online remote data entry (eRDE) system– at the protocol specified time point. In order to enter a patient into the trial an appropriate eligibility checklist must be completed. See Eligibility sections for details.

For each randomisation, the randomisation program will allocate treatment via a computerised minimisation algorithm, developed by CRCTU. All of the required information on stratification factors must be available at the time of randomisation.

https://v4.viedoc.net/Login

Refer to FaR-RMS Site CRF Completion Data Management Guidelines for more details.

A confirmation of Study Entry and entry to each trial randomisation/registration should be printed and retained in the ISF and the patient's hospital records.

If allowed by country specific legislation/guidance, a copy of the patient's ICF must be sent to the applicable NCC, if explicit consent has been given for this.

6.2 Emergency Registration/ Randomisation

In case of any problems with the online system, the appropriate eligibility checklist and Study Entry/ Registration/Randomisation forms should be completed. These details can be phoned through to the UK Coordinating Centre at CRCTU using the numbers below:

STUDY ENTRY/ RANDOMISATION

(09:00 to 17:00 GMT / BST, Monday to Friday)

☎ +44 (0)121 415 1060/ (0)121 414 2996

7. STUDY ENTRY

FaR-RMS includes a study entry point where **all** patients with RMS may give consent for the analysis of their biological samples and tumour pathology, alongside the collection of very basic patient characteristics, a treatment summary, and follow-up data for events.

Newly diagnosed patients should where possible be entered into the FaR-RMS study at the time of first diagnosis prior to receiving any chemotherapy. However, patients can also be entered at the point of radiotherapy, maintenance or relapse randomisations. Exceptionally, patients may be entered at any other time point.

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7.1 Eligibility Criteria

7.1.1 Inclusion Criteria for study entry

Mandatory at first point of study entry

1. Histologically confirmed diagnosis of RMS (except pleomorphic RMS)
2. Written informed consent from the patient and/or the parent/legal guardian

8. PHARMACY

The following drugs are regarded as Investigational Medicinal Products (IMPs) for the purposes of this trial:

- Actinomycin D (dactinomycin)
- Doxorubicin
- Ifosfamide
- Irinotecan
- Vincristine
- Vinorelbine (i.v)

- Vinorelbine (oral)
- Cyclophosphamide (i.v)
- Cyclophosphamide (oral liquid) – where licensed formulation available, or method of preparation approved
- Cyclophosphamide (oral tablet)
- Temozolomide
- Regorafenib (tablet)
- Regorafenib (granules)

During maintenance vinorelbine and cyclophosphamide will only be IMPs following commencement of randomised treatment.

Regorafenib will be supplied free of charge by Bayer for use in this trial. Full details of supply, storage preparation, labelling and accountability are contained in the national Pharmacy Manual. Country specific requirements for the safe handling of medicines must be adhered to.

All other IMPs are expected to be held as routine hospital stock and should therefore be stored and handled according to local institutional policy. Labels will be produced by each NCC in accordance with national guidelines and legislation.

Drugs should be prepared and administered according to the relevant Summary of Product Characteristics (SmPC) and local practice, unless the trial protocol requires otherwise.

Please also see the country specific Pharmacy Manual for further details.

New IMPs may be added as new agents become available and added to the MAMs design of the study. An application for substantial amendment will be submitted to the regulatory authorities for approval before addition of any new IMPs.

8.1 Dose capping

Vincristine and actinomycin D should be capped at the maximum dose of 2mg in all cases.

All other doses listed should be capped according to institutional practice (e.g. 90th centile by age for children and 2m^2 for adults).

9. PHASE IB COMBINATION DOSE FINDING (RECRUITMENT COMPLETE)

A Rolling-6 escalation design will be used. Escalation/de-escalation decisions will be based on the DLTs that occur during the defined time period. The Rolling-6 design is consistent with the rules of the traditional 3+3 escalation design except that enrolment to a dose level will continue until up to 6 patients have been treated in line with the following rules:

Escalation to the next dose level may occur if at least 3 patients have been treated and no evaluated patients have experienced a DLT. In the case of 1 DLT in the first 3 patients, the cohort will be expanded to a minimum of 6 patients before a decision for dose escalation. If more than one DLT occurs in the first cohort, dose level -1 will be evaluated.

The Maximum Tolerated Dose (MTD) is the highest dose level tested at which no or one patient (out of six) experiences DLT during course 1 with at least 2 patients experiencing DLT at the next higher dose. If the highest specified dose level is reached with no or one patient (out of six) experiencing

DLT – i.e. the MTD has not been reached – this dose level will be referred to as the highest tested dose.

For each cohort, the recommendation whether or not to dose-escalate in the next cohort or to declare the MTD/RP2D will be made by the Data Monitoring Committee (DMC). The DMC will review all available clinical laboratory and safety data for a given cohort and, if applicable, data from previous cohorts.

Phase 1b will be conducted in selected paediatric/adolescent early phase trial centres.

Phase 1b is intended to be a rolling programme to determine the RP2D of therapy combinations in patients with RMS. Where the clinical activity of the new treatment regimen is unknown or requires further investigation, a single arm expansion, Phase II, cohort to obtain an assessment of activity, will follow-on from the determination of the RP2D. The expansion cohort will be designed on an arm by arm basis.

Suspected DLTs must be reported to the UK Coordinating Centre by email or phone immediately upon awareness of the event. The DLT form must then be completed on the eRDC and a paper copy, signed by an investigator sent via email to FaR-RMS@trials.bham.ac.uk or Fax to +44 (0)121 414 9520

9.1 Eligibility Criteria

9.1.1 Inclusion

1. Entered in to the FaR-RMS study at diagnosis
2. VHR disease
3. Age >12 months and ≤25 years
4. No prior treatment for RMS other than surgery
5. Medically fit to receive treatment
6. Adequate hepatic function:
    a. Total bilirubin ≤ 1.5 times upper limit of normal (ULN) for age, unless the patient is known to have Gilbert's syndrome
    b. ALT or AST < 2.5 X ULN for age
7. Absolute neutrophil count ≥1.0x 10^9/L
8. Platelets ≥ 80 x 10^9/L
9. Adequate renal function: estimated or measured creatinine clearance ≥60 ml/min/1.73 m^2
10. Documented negative pregnancy test for female patients of childbearing potential
11. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active
12. Written informed consent from the patient and/or the parent/legal guardian

9.1.2 Exclusion

1. Weight <10kg
2. Active > grade 2 diarrhoea
3. Prior allo- or autologous Stem Cell Transplant
4. Uncontrolled intercurrent illness or active infection
5. Pre-existing medical condition precluding treatment
6. Urinary outflow obstruction that cannot be relieved prior to starting treatment
7. Active inflammation of the urinary bladder (cystitis)
8. Known hypersensitivity to any of the treatments or excipients
9. Second malignancy
10. Pregnant or breastfeeding women

9.2 Phase Ib Assessments

See Table 6: Schedule of Assessments for new diagnosed frontline patient

9.3 Phase Ib Irinotecan dose finding treatment schedule

The phase Ib Irinotecan dose finding study will investigate the addition of irinotecan to IVA (I_RIVA). Patients with VHR disease will be eligible. The patients will receive standard doses of IVA with the addition of a 5-day schedule of irinotecan in a rolling 6 design. Irinotecan will be delivered at the dose specified on days 8-12 of each 21 day cycle. Up to 9 cycles in total will be given to each patient if tolerated. Dose limiting toxicities (DLTs) will be assessed in Cycles 1 and 2. See APPENDIX 1 for further information.

Table 4: I_RIVA treatment schedule

Cycles of chemotherapy will be given at 21 day intervals providing there is haematological recovery to ANC ≥1.0 x 10^9/L, platelets ≥80 x 10^9/L. See APPENDIX 1.i and APPENDIX 1.ii for further information.

I_RIVA : 21 day cycle. 9 cycles in total			
		Daily dose	
Irinotecan	Days 8, 9, 10, 11 & 12	Dose assigned according to Table 5	As per local practice, recommended as an i.v infusion over 1 hour.
Ifosfamide	Days 1 & 2	3g/m^2	As an i.v infusion, timing as per local practice: recommended over 3 hours, with mesna and hydration given according to institutional practice.
Vincristine	Days 1, 8 & 15 **(Cycles 1 & 2 ONLY).**	1.5mg/m^2	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Vincristine	Day 1 and 8 (Cycle 3,4,5,6,7,8,9).	1.5mg/m^2	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Actinomycin D	Day 1.	1.5mg/m^2	As per local practice: recommended as an i.v bolus injection Maximum dose: 2mg.
Cefixime* or equivalent	Day 6 to Day 14	by mouth	Recommended (but not mandated) for prophylaxis of irinotecan-induced diarrhoea.

*for cefixime recommended dose is 8mg/kg once daily by mouth, maximum dose: 400mg

Cyclophosphamide cannot replace ifosfamide during Phase 1b

G-CSF should not be given during the first 2 cycles of treatment.

Dose-escalation scheme specifics are outlined below. For the purposes of the irinotecan dose-escalation, DLTs will be assessed during the first 2 cycles of treatment, which is defined as the period from the start of trial treatment to 21 days after the start of cycle 2.

Table 5: Dose escalation/de-escalation for irinotecan

Dose Level irinotecan	Dose	Route	Days
-1	10mg/m^2	iv in 1 hour	Day 8-12
1 (starting dose)	20mg/m^2	iv in 1 hour	Day 8-12
2	30mg/m^2	iv in 1 hour	Day 8-12
3	40mg/m^2	iv in 1 hour	Day 8-12
4	50mg/m^2	iv in 1 hour	Day 8-12

9.3.1 Dose modifications during phase 1b

No dose modifications should be made during cycles 1 and 2 of treatment.

*Patients starting on a certain dose level without DLT should stay on that dose for all 9 cycles. There should be no intra-patient dose escalation even if the known safe dose is higher than the dose the patient is receiving. In the event that a patient experiences a DLT in cycle 1 or cycle 2, the patient should receive the standard of care for subsequent cycles.

After cycles 1 and 2 refer to Section 12 for dose modifications.

See section 13 for warnings and section 15 for a list of prohibited concomitant medications

9.3.2 Definition of Dose-Limiting Toxicity

Adverse events will be graded according to the NCI CTCAE v4. A DLT will be defined as any of the following haematological and non-haematological events that occur during the DLT period (21 days after the start of cycle 2 or 28 days after the start of cycle 2 for persistent neutropenia or thrombocytopenia) and are at least possibly related (possibly, probably, or definitely) attributable to IRIVA.

- Diarrhoea: Grade 3 (increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living) for >3 days despite loperamide therapy
- Diarrhoea: Grade 4 (life-threatening consequences; urgent intervention indicated) despite loperamide therapy.
- Enterocolitis: Grade 3 (interpreted as combination of severe or persistent abdominal pain, fever, ileus, peritoneal signs) or above
- Ileus: Grade 3 (severely altered GI function, parenteral nutrition indicated) or above for more than 3 days
- Oral mucositis: Grade 3 (severe pain; interfering with oral intake) or above for >3 days despite optimal supportive care
- Persistent neutropenia or thrombocytopenia (ANC <1.0 x 10^9/L, platelets <80 x 10^9/L) leading to delay of start of next course by >7 days; i.e. starting > day 28
- Any grade 3 or 4 toxicity resulting in discontinuation of the new combination
- Any grade 5 toxicity related to study treatment (death)

10. FRONTLINE (NEWLY DIAGNOSED) PATIENTS

10.1 Frontline Assessments

The following are the required assessments and monitoring before and during treatment for all patients registered to phase 1b or randomised to CT1a, CT1b, CT2a and CT2b. Further monitoring can be performed according to institutional guidance.

Table 6: Schedule of Assessments for new diagnosed frontline patient

	Screening (28 days)	**INDUCTION THERAPY Cycles 1-9**			**Screening CT2** (28 days)	**MAINTENANCE THERAPY** HR: STOP or + 6 cycles: (continuing cycles 7-12) VHR: STOP or +12 cycles: (continuing cycles 13-24)			**Relapse**	**Follow-up**
		Prior 3 days	**During**	**After**		**Prior** 3 days	**During**	**After**		
Informed Consent	•				•					
Trial Entry *Registration/ Randomisation* Projected start date of treatment should be no later than 5 days from randomisation.		Prior to cycle 1			Randomisation during VHR: cycle 12 HR: cycle 6					
Demographics	•									
Medical history	•									
Clinical Exam (to include neurological examination and vital signs)[a]	•	•			•	•				•
Cryopreservation as per local practice	•									
Assessment for active Infection[b]	•									
Pregnancy Test[c]	•	•			•	•				•
Haematology *(as standard of care)*	•	•	As clinically indicated		•	•	As clinically indicated – including vinorelbine titration			
Blood Biochemistry *(as standard of care, to include liver function and serum creatinine tests)*	•	•	As clinically indicated		•	•	As clinically indicated			
(e)GFR and Tubular Function[d]	•	Cycle 1 then as per institutional guidelines	As clinically indicated			•	As clinically indicated			
Echocardiography [e]	•		After 3 cycles then as clinically indicated							•

	Screening (28 days)	INDUCTION THERAPY Cycles 1-9			Screening CT2 (28 days)	MAINTENANCE THERAPY HR: STOP or + 6 cycles: (continuing cycles 7-12) VHR: STOP or +12 cycles: (continuing cycles 13-24)			Relapse	Follow-up
		Prior 3 days	During	After		Prior 3 days	During	After		
Staging as per local practice [h]	•									
Imaging tumour site(s) [f]	•			After cycles 3, 9, (And after 6 for group H)	•		Every 3-4 months for all patients (randomised to stop or continue)		•	•
CT Chest [g]	•		If positive, after 3 cycles repeat after cycle 6	If positive at staging repeat , at end of treatment			As clinically indicated	As clinically indicated		
FDG-PET CT/MRI [h]	•	As per local practice FDG-PET sub-study patients : After cycle 3								
Histological Diagnosis	•	National Central Pathology Review								
Fusion Status	•									
Fresh frozen tumour *(strongly recommended)*	•									
BM Aspirate/trephine biopsy[i] *(as standard of care)*	•		If positive, after cycles 3, 6, 9 or until negative							
CSF Cytology[j]	•									
Quality of Life		See Radiotherapy Section								
Biobanking	Recommended as per national practice									
Adverse Event reporting			Throughout the entire treatment phase							
CRF Completion			Throughout trial duration							

a. For example: temperature, blood pressure, heart rate, respiratory rate.
b. Assessment to include testing for Hepatitis B, C and HIV in patients with deranged liver function and/or HIV if clinically indicated.
c. A highly sensitive test: for female patients of child bearing potential only. Screening pregnancy test to be carried out within 14 days of starting treatment. Ongoing pregnancy tests are required during protocol defined treatment, recommended prior to each cycle and monthly up to 12 months after last treatment.
d. To be monitored more frequently in patients with impaired renal function.
e. VHR only: echocardiogram required for all patients at baseline. Repeat assessment during treatment only required for patients who receive doxorubicin.
f. MRI is recommended. Use same mode of investigation of tumour sites throughout study. See 10.6.3 and 10.7.3 for scan requirements prior to maintenance randomisation.
g. Repeat chest CT only if there is pulmonary involvement at diagnosis.
h. Staging as per local practice; i.e. FDG PET CT is the investigation of choice, otherwise as per local practice. Use same mode of investigation throughout study. Recommended to repeat in case of FDG-PET positive lymph nodes or FDG-PET positive distant metastases at diagnosis until negative or after local therapy. Patients that participate in the FDG-PET response study will have their scan repeated after cycle 3. FDG-PET negative at diagnosis do not need to be repeated.
i. Only if positive at diagnosis.
j. Primary tumours with a parameningeal location only – if positive, repeat as standard of care.

10.2 Very High Risk: CT1^{A} Induction Chemotherapy

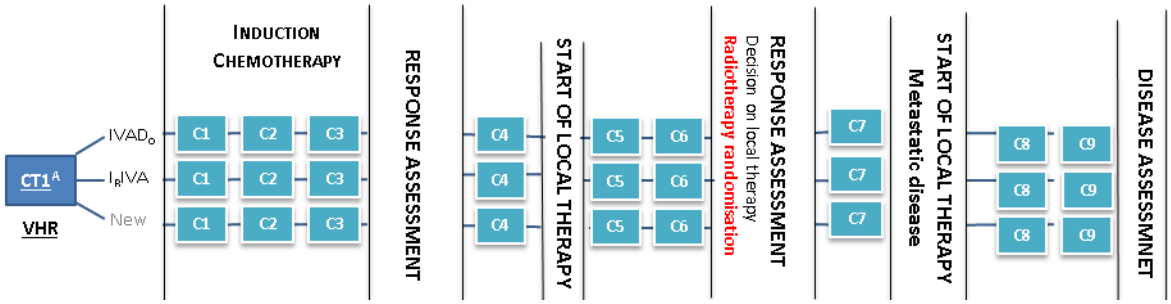
Newly diagnosed VHR patients will be randomised to receive either IVADo (Ifosfamide, Vincristine, Actinomycin D, Doxorubicin) or I$_R$IVA (Irinotecan, Ifosfamide, Vincristine, Actinomycin D).

~~This randomisation will open following completion of the Phase 1b of I$_R$IVA. Prior to the randomisation opening, patients should be treated in accordance with the current standard of care- (i.e. IVADo based regimen unless there is a clinical contraindication to any of the agents).~~

The first 6 patients > 18 years randomised to I$_R$IVA (from either the VHR or HR randomisations) will be carefully evaluated by the Data Monitoring Committee (DMC) before continuing the randomisation in adult patients in view of the fact that the phase Ib study is likely to include disproportionately more children than young adults.

Patients 6 months to ≤12 months will be dosed by mg/kg. See APPENDIX 4. The first 3 patients randomised to I$_R$IVA (from either the VHR or HR randomisations) will be carefully evaluated by the DMC.

Figure 5: VHR CT1^{A} schema



10.2.1 Inclusion

1. Entered in to the FaR-RMS study at diagnosis
2. VHR disease
3. Age ≥ 6 months
4. Planned date of randomisation ≤60 days after diagnostic biopsy/surgery
5. No prior treatment for RMS other than surgery
6. Medically fit to receive treatment
7. Adequate hepatic function:
    a. Total bilirubin ≤ 1.5 times upper limit of normal (ULN) for age, unless the patient is known to have Gilbert's syndrome
8. Absolute neutrophil count ≥1.0x 10^9/L (except in patients with documented bone marrow disease)
9. Platelets ≥ 80 x 10^9/L (except in patients with documented bone marrow disease)
10. Fractional Shortening ≥ 28%
11. Documented negative pregnancy test for female patients of childbearing potential
12. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active
13. Written informed consent from the patient and/or the parent/legal guardian

10.2.2 Exclusion

1. Active > grade 2 diarrhoea
2. Prior allo- or autologous Stem Cell Transplant
3. Uncontrolled inter-current illness or active infection

4. Pre-existing medical condition precluding treatment
5. Urinary outflow obstruction that cannot be relieved prior to starting treatment
6. Active inflammation of the urinary bladder (cystitis)
7. Known hypersensitivity to any of the treatments or excipients
8. Second malignancy
9. Pregnant or breastfeeding women

10.2.3 Assessments

See Table 6: Schedule of Assessments for new diagnosed frontline patient

10.2.4 CT1^{A} Treatment schedules

Cycles of chemotherapy will be given at 21 day intervals providing there is haematological recovery to ANC ≥1.0 x 10^9/L, platelets ≥80 x 10^9/L. See APPENDIX 1. and APPENDIX 1.ii for further information.

Patients 6 months to ≤12 months: Will be dosed by mg/kg - see appendix APPENDIX 4. The first 3 patients randomised to I_RIVA (from either the VHR or HR randomisations) will be carefully evaluated by the DMC.

Vincristine and Actinomycin D should be capped at the maximum dose of 2mg in all cases.

All other doses listed should be capped according to institutional practice (e.g. 90th centile by age for children and 2m^2 for adults).

IVADo	**21 day cycle. 9 cycles in total**		
		Daily dose	
Ifosfamide	Days 1 & 2	3g/m^2	As an i.v infusion, timing as per local practice: recommended over 3 hours, with mesna and hydration given according to institutional practice.
Vincristine	Days 1, 8 & 15 **(Cycles 1 & 2 ONLY).**	1.5mg/m^2	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Vincristine	Day 1 (Cycle 3,4,5,6,7,8,9).	1.5mg/m^2	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Actinomycin D **should be omitted during and for 2 weeks after delivery of radiotherapy**	Day 1	1.5mg/m^2	As per local practice: recommended as an i.v bolus injection Maximum dose: 2mg.
Doxorubicin **should not be given concomitantly with radiotherapy**	Days 1 & 2 Cycles 1,2,3,4 only	30mg/m^2	As an i.v infusion, timing as per local practice: recommended over 1 hour

Substitution

Cyclophosphamide	Day 1	1500 mg/m^2	As an i.v infusion, timing as per local practice: recommended over 1 hour, with mesna and hydration given according to institutional practice
Cyclophosphamide may replace ifosfamide in patients with clinical indications such as significant renal dysfunction			

I_RIVA	**21 day cycle. 9 cycles in total**		
Irinotecan	Days 8,9,10,11 &12	50mg/ m^2	As an i.v infusion timing as per local practice: recommended over 1 hour
Ifosfamide	Days 1 & 2	3g/m^2	As an i.v infusion, timing as per local practice: recommended over 3 hours, with mesna and hydration given according to institutional practice.
Vincristine	**Days 1, 8 & 15 (Cycles 1 & 2 ONLY).**	1.5mg/m^2	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Vincristine	Day 1 and 8 (Cycle 3,4,5,6,7,8,9).	1.5mg/m^2	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Actinomycin D **should be omitted during and for 2 weeks after delivery of radiotherapy**	Day 1.	1.5mg/m^2	As per local practice: recommended as an i.v bolus injection Maximum dose: 2mg.
Cefixime* or equivalent	Day 6 to Day 14	mouth	Recommended (but not mandated) for prophylaxis of irinotecan-induced diarrhoea.

*for cefixime recommended dose is 8mg/kg once daily by mouth, maximum dose: 400mg

Substitution

Cyclophosphamide	Day 1	1500 mg/m^2	As an i.v infusion, timing as per local practice: recommended over 1 hour, with mesna and hydration given according to institutional practice
Cyclophosphamide may replace ifosfamide in patients with clinical indications such as significant renal dysfunction			

10.2.5 CT1^A Dose Modifications

See APPENDIX 3 and APPENDIX 4 for dose modifications for smaller/younger patients

See section 12 for dose modifications due to toxicity.

10.2.6 CT1[A] Prohibited Medications

See section13 for warnings and section 15 for a list of prohibited concomitant medications

10.3 High Risk: CT1^{B} Induction Chemotherapy

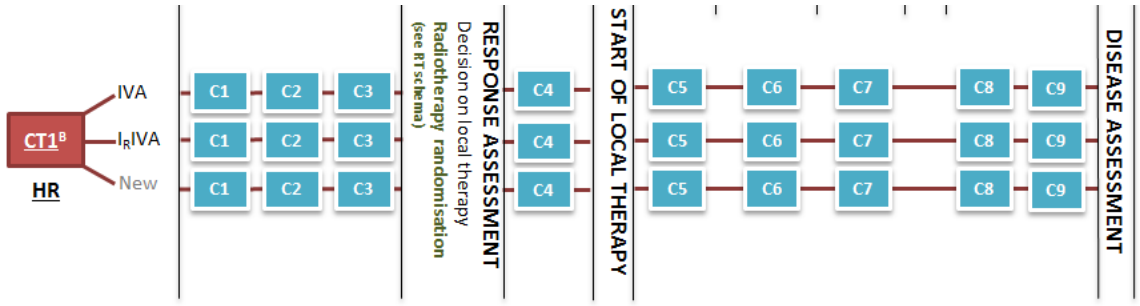
Newly diagnosed HR patients will be randomised to receive either IVA (Ifosfamide, Vincristine, Actinomycin D) or I$_R$IVA (Irinotecan, Ifosfamide, Vincristine, Actinomycin D)

This randomisation will open following completion of the Phase 1b of I$_R$IVA. Prior to the randomisation patients should be treated in accordance with the current standard of care.

The first 6 patients > 18 years randomised to I$_R$IVA (from either the VHR or HR randomisations) will be carefully evaluated by the DMC before continuing the randomisation in adult patients in view of the fact that the phase Ib study is likely to include disproportionately more children than young adults.

Patients 6 months to ≤12 months will be dosed by mg/kg. See APPENDIX 4. The first 3 patients randomised to I$_R$IVA (from either the VHR or HR randomisations) will be carefully evaluated by the DMC.

Figure 6: HR CT1^{B} schema



10.3.1 Inclusion

1. Entered in to the FaR-RMS study at diagnosis
2. HR disease
3. Age ≥ 6 months
4. Available for randomisation ≤60 days after diagnostic biopsy/surgery
5. No prior treatment for RMS other than surgery
6. Medically fit to receive treatment
7. Adequate hepatic function:
    a. Total bilirubin ≤ 1.5 times upper limit of normal (ULN) for age, except if the patient is known to have Gilbert's syndrome
8. Absolute neutrophil count ≥1.0x 10^9/L
9. Platelets ≥ 80 x 10^9/L
10. Documented negative pregnancy test for female patients of childbearing potential
11. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active
12. Written informed consent from the patient and/or the parent/legal guardian

10.3.2 Exclusion

1. Active > grade 2 diarrhoea
2. Prior allo- or autologous Stem Cell Transplant
3. Uncontrolled inter-current illness or active infection
4. Pre-existing medical condition precluding treatment
5. Urinary outflow obstruction that cannot be relieved prior to starting treatment
6. Active inflammation of the urinary bladder (cystitis)

7. Known hypersensitivity to any of the treatments or excipients
8. Second malignancy
9. Pregnant or breastfeeding women

10.3.3 Assessments

See Table 6: Schedule of Assessments for new diagnosed frontline patient

10.3.4 CT1^{B} Treatment schedules

Please see APPENDIX 1.iii for further details.

Patients 6 months to ≤12 months: Will be dosed by mg/kg see appendix APPENDIX 4. The first 3 patients randomised to I$_R$IVA (from either the VHR or HR randomisations) will be carefully evaluated by the DMC.

Cycles of chemotherapy will be given at 21 day intervals providing there is haematological recovery to ANC ≥1.0 x 109/L, platelets ≥80 x 109/L. See APPENDIX 1.i and APPENDIX 1.ii for further information

Vincristine and Actinomycin D should be capped at the maximum dose of 2mg in all cases.

All other doses listed should be capped according to institutional practice (e.g. 90th centile by age for children and 2m^2 for adults).

IVA	**21 day cycle. 9 cycles in total**		
		Daily dose	
Ifosfamide	Days 1 & 2	3g/m^2	As an i.v infusion, timing as per local practice: recommended over 3 hours, with mesna and hydration given according to institutional practice.
Vincristine	Days 1, 8 & 15 **(Cycles 1 & 2 ONLY).**	1.5mg/m^2	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Vincristine	Day 1 (Cycle 3,4,5,6,7,8,9)..	1.5mg/m^2	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Actinomycin D **Should be omitted during and for 2 weeks after delivery of radiotherapy**	Day 1.	1.5mg/m^2	As per local practice: recommended as an i.v bolus injection Maximum dose: 2mg.

Substitution

Cyclophosphamide	Day 1	1500 mg/m^2	As an i.v infusion, timing as per local practice: recommended over 1 hour, with mesna and hydration given according to institutional practice
Cyclophosphamide may replace ifosfamide in patients with clinical indications such as significant renal dysfunction			

I_RIVA	**21 day cycle. 9 cycles in total**		
Irinotecan	Days 8,9,10,11 &12	50mg/ m^2	As an i.v infusion, timing as per local practice: recommended over 1 hour
Ifosfamide	Days 1 & 2	3g/m^2	As an i.v infusion, timing as per local practice: recommended over 3 hours, with mesna and hydration given according to institutional practice.
Vincristine	Days 1, 8 & 15 **(Cycles 1 & 2 ONLY).**	1.5mg/m^2	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Vincristine	Day 1 and 8 (Cycle 3,4,5,6,7,8,9).	1.5mg/m^2	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Actinomycin D **Should be omitted during and for 2 weeks after delivery of radiotherapy**	Day 1.	1.5mg/m^2	As per local practice: recommended as an i.v bolus injection Maximum dose: 2mg.
Cefixime * or equivalent	Day 6 to Day 14	by mouth	Recommended (but not mandated) for prophylaxis of irinotecan-induced diarrhoea.

*for cefixime recommended dose is 8mg/kg once daily by mouth, maximum dose: 400mg

Substitution

Cyclophosphamide	Day 1	1500 mg/m^2	As an i.v infusion, timing as per local practice: recommended over 1 hour, with mesna and hydration given according to institutional practice
Cyclophosphamide may replace ifosfamide in patients with clinical indications such as significant renal dysfunction			

10.3.5 CT1^{B} Dose Modifications

See APPENDIX 3 and APPENDIX 4 for dose modifications for smaller/younger patients

See section 12 for dose modifications due to toxicity.

10.3.6 CT1^{B} Prohibited Medications

See section 13 for warnings and section 15 for a list of prohibited concomitant medications

10.4 Standard Risk Induction Chemotherapy

SR patients should receive induction chemotherapy according to current standard practice. A suggested regimen can be found in the Standard Risk Induction Chemotherapy Guidelines (see APPENDIX 2 for more details). Such treatment is given as off-trial treatment. Deviations from the suggested treatment schedule and dose modifications are not deviations from the protocol.

SR patients should be considered for radiotherapy randomisations.

10.5 Timing of local therapy

The decision to proceed to local therapy (surgery and/or radiotherapy) should be made after 3 cycles of induction chemotherapy (or after 6 cycles for patients with metastatic disease). Where a patient is deemed suitable for radiotherapy, radiotherapy randomisations should be considered, see Section 16 for further details of eligibility and timings.

See EpSSG Surgical and Radiotherapy guidelines for patients with RMS. See APPENDIX 14 for further details.

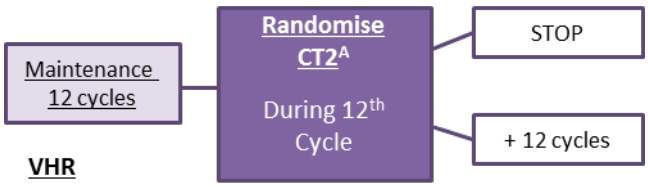
10.6 Very High Risk: CT2^{A} Maintenance Chemotherapy

Patients in complete remission or with no evidence of active residual disease on imaging studies at the end of front line treatment should commence maintenance treatment within 8 weeks of commencing the last cycle of frontline chemotherapy.

VHR patients will receive 12 cycles of maintenance chemotherapy as standard of care. They may then be eligible for randomisation to either stop treatment or receive 12 further cycles of maintenance chemotherapy.

Eligible patients must be consented and then be randomised during the 12th cycle of maintenance chemotherapy.

Figure 7: VHR CT2^{A} schema



10.6.1 Inclusion

1. Entered in to the FaR-RMS study (at diagnosis or at any subsequent time point)
2. VHR disease
3. Received frontline induction chemotherapy as part of the FaR-RMS trial or with a IVA/ IVADo based chemotherapy regimen
    a. Patients for whom ifosfamide has been replaced with cyclophosphamide will be eligible
4. Completed 11 cycles of VnC maintenance treatment (either oral or IV regimens)
5. No evidence of progressive disease
6. Absence of severe vincristine neuropathy – i.e. requiring discontinuation of vincristine treatment
7. Medically fit to continue to receive treatment
8. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active
9. Written informed consent from the patient and/or the parent/legal guardian

10.6.2 Exclusion

1. Prior allo- or autologous Stem Cell Transplant
2. Uncontrolled inter-current illness or active infection
3. Urinary outflow obstruction that cannot be relieved prior to starting treatment
4. Active inflammation of the urinary bladder (cystitis)
5. Second malignancy
6. Pregnant or breastfeeding women

10.6.3 Assessments

A radiological assessment should be conducted after 11 cycles of maintenance treatment to confirm that there is no evidence of disease progression at the point of entry to CT2^{A} (during 12th cycle)

SeeTable 6: Schedule of Assessments for new diagnosed frontline patient

Patients who are randomised to stop treatment should be followed-up as per local practice – see section 22

10.6.4 CT2[A] Treatment schedules

The vinorelbine and cyclophosphamide (VC) regimen is given during maintenance. Both intravenous (i.v.) and oral vinorelbine regimens are permissible. Please see Appendix 1.iv for further information.

Suggested regimens are provided below:

10.6.4.1 Intravenous vinorelbine and oral cyclophosphamide:

Each 28 day cycle of VnC comprises vinorelbine 25 mg/m^2 IV over 5-10 minutes on days 1, 8 and 15, and cyclophosphamide 25 mg/m^2 orally daily for 28 days; no rest between cycles.

Cycles of chemotherapy will be given at 28 day intervals providing there is evidence of haematological recovery to ANC ≥1.0 x 10^9/L, platelets ≥80 x 10^9/L and in the absence of any relevant organ dysfunction.

For oral cyclophosphamide dosing chart – see APPENDIX 6

The maximum intravenous dose of vinorelbine per administration is 60mg

10.6.4.2 Oral vinorelbine and oral cyclophosphamide

Each 28 day cycle of VnC comprises vinorelbine 60 mg/m^2 orally on days 1, 8 and 15, and cyclophosphamide 25 mg/m^2 orally daily for 28 days; no rest between cycles.

Cycles of chemotherapy will be given at 28 day intervals providing there is evidence of haematological recovery to ANC ≥1.0 x 10^9/L, platelets ≥80 x 10^9/L. Doses of vinorelbine and cyclophosphamide may also be modified during cycles of maintenance chemotherapy, depending on blood count (usually done weekly, prior to vinorelbine dose).

For oral vinorelbine dosing chart – see APPENDIX 5

For oral cyclophosphamide dosing chart – see APPENDIX 6

For patients with BSA ≥ 2 m^2 the total dose should never exceed 120 mg per week at 60 mg/m^2

10.6.5 CT2[A] Dose Modifications

See APPENDIX 3 and APPENDIX 4 for dose modifications for smaller/younger patients

Blood count (neutrophils and platelets) should be measured weekly until a stable maintenance regime has been established.

Once established a full blood count every two weeks, just prior to day 1 and 15 vinorelbine, is sufficient.

Patients randomised to continue will maintain the dose established during standard of care maintenance.

Doses of vinorelbine and cyclophosphamide may also be modified during cycles of maintenance chemotherapy, depending on blood count (neutrophils and platelets) taken the week prior to vinorelbine dose.

Hematologic toxicity occurs frequently during maintenance, mainly neutropenia. Predominantly during the first cycles because of radiation therapy-associated toxicity but can occur anytime during maintenance.

In case of neutropenia (<0.75 x109/L neutrophils) and/or thrombocytopenia (< 80 x109/L platelets), cyclophosphamide and vinorelbine should be interrupted until count recovery.

Vinorelbine should be administered at day 1 and 15 (omitting the second dose) for the subsequent cycle and escalated each cycle as tolerated.

In case of neutropenia before day 8, consider a dose reduction on day 1 of the next cycle.

In case of further haematological toxicity, cyclophosphamide may be administered at 66% of the previous dose and escalated to find a dose that can be tolerated alongside a dose of vinorelbine on Days 1, and 15.

In case of further haematological toxicity, vinorelbine should be administered at 66% dose at day 1 and 15.

In case of need for interruption of chemotherapy, next blood count should be after one week of chemotherapy interruption and followed until recovery. When chemotherapy is resumed, start with oral cyclophosphamide and the next planned dose of vinorelbine in the 4 weekly cycle, without making up missed doses of either drug. See section 12 for dose modifications due to other toxicity.

10.6.6 CT2^{A} Prohibited Medications

See section 13 for warnings and section 15 for a list of prohibited concomitant medications

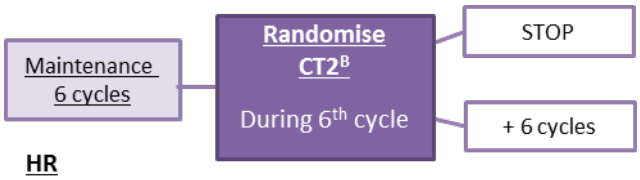
10.7 HR: CT2^{B} Maintenance Chemotherapy

Patients in complete remission or with minimal abnormalities (no evidence of active residual disease on imaging at the end of front line treatment) on imaging studies at the end of frontline treatment should commence maintenance treatment within 8 weeks of commencing the last cycle of frontline chemotherapy.

HR patients should receive 6 cycles of maintenance chemotherapy (intravenous vinorelbine, oral cyclophosphamide) as standard of care. They may then be eligible for randomisation to either stop treatment or receive 6 further cycles of maintenance chemotherapy (intravenous vinorelbine, oral cyclophosphamide).

Eligible patients must consent and then be randomised during the 6th cycle of maintenance chemotherapy.

Figure 8: HR CT2^{B} schema



10.7.1 Inclusion

1. Entered in to the FaR-RMS study (at diagnosis or at any subsequent time point)
2. HR disease
3. Received frontline induction chemotherapy as part of the FaR-RMS trial or with a IVA based chemotherapy regimen. Patients for whom ifosfamide has been replaced with cyclophosphamide will be eligible
4. Completed 5 cycles of VnC maintenance treatment
5. No evidence of progressive disease
6. Absence of severe vincristine neuropathy i.e. requiring discontinuation of vincristine treatment
7. Medically fit to continue to receive treatment
8. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active
9. Written informed consent from the patient and/or the parent/legal guardian

10.7.2 Exclusion

1. Prior allo- or autologous Stem Cell Transplant
2. Uncontrolled inter-current illness or active infection
3. Urinary outflow obstruction that cannot be relieved prior to starting treatment
4. Active inflammation of the urinary bladder (cystitis)
5. Second malignancy
6. Pregnant or breastfeeding women

10.7.3 Assessments

A radiological assessment should be conducted after 5 cycles of maintenance treatment to confirm that there is no evidence of disease progression at the point of entry to $CT2^B$ (during 6^{th} cycle)

See Table 6: Schedule of Assessments for new diagnosed frontline patient

10.7.4 $CT2^B$ Treatment schedules

Intravenous vinorelbine and oral cyclophosphamide:

Each 28 day cycle of VnC comprises vinorelbine 25 mg/m^2 i.v. over 5-10 minutes on days 1, 8 and 15, and cyclophosphamide 25 mg/m^2 orally daily for 28 days; no rest between cycles.

Cycles of chemotherapy will be given at 28 day intervals providing there is evidence of haematological recovery to ANC ≥1.0 x 10^9/L, platelets ≥80 x 10^9/L and in the absence of any relevant organ dysfunction.

For further information please see APPENDIX 1.v

For oral cyclophosphamide dosing chart – see APPENDIX 6

The maximum intravenous dose of vinorelbine per administration is 60mg

10.7.5 CT2[B] Dose Modifications

See APPENDIX 3 and APPENDIX 4 for dose modifications for smaller/younger patients.

Blood count (neutrophils and platelets) should be measured weekly until a stable maintenance regime has been established.

Once established a full blood count every two weeks, just prior to day 1 and 15 vinorelbine, is sufficient.

Patients randomised to continue will maintain the dose established during standard of care maintenance.

Doses of vinorelbine and cyclophosphamide may also be modified during cycles of maintenance chemotherapy, depending on blood count (neutrophils and platelets) taken the week prior to vinorelbine dose.

Hematologic toxicity occurs frequently during maintenance, mainly neutropenia. Predominantly during the first cycles because of radiation therapy-associated toxicity but can occur anytime during maintenance.

In case of neutropenia (<0.75 $x10^9$/L neutrophils) and/or thrombocytopenia (< 80 $x10^9$/L platelets), cyclophosphamide and vinorelbine should be interrupted until count recovery.

Vinorelbine should be administered at day 1 and 15 (omitting the second dose) for the subsequent cycle and escalated each cycle as tolerated.

In case of neutropenia before day 8, consider a dose reduction on day 1 of the next cycle.

In case of further haematological toxicity, cyclophosphamide may be reintroduced at 66% of the previous dose and escalated each week as tolerated to find a dose that can be tolerated alongside a weekly dose of vinorelbine on Days 1and 15.

In case of further haematological toxicity, vinorelbine should be administered at 66% dose at day 1 and 15.

In case of need for interruption of chemotherapy, next blood count should be after one week of chemotherapy interruption and followed until recovery. When chemotherapy is resumed, start with oral cyclophosphamide and the next planned dose of vinorelbine in the 4 weekly cycle, without making up missed doses of either drug.

See section 12 for dose modifications due to other toxicity.

10.7.6 CT2[B] Prohibited Medications

See section 13 for warnings and section15 for a list of prohibited concomitant medications.

11. RELAPSED RMS – CT3

11.1 CT3 Relapsed Assessments

The following are the required assessments and monitoring before and during treatment. Further monitoring can be performed according to institutional guidance. All assessments must be documented in the source data but only those data items which are required for safety and efficacy will be collected on the case report forms.

Table 7: Schedule of Assessments for relapsed patients

	Screening <28 days or as indicated	**Chemotherapy - per cycle** 12 cycles, 21 day cycles			**30 days after end of Treatment**	**Follow-up (5 year minimum)**
		Prior 3 days	**During**	**After**		
Informed consent	•					
Randomisation		prior to cycle 1				
Demographics	•					
Medical history and prior therapy	•					
Height	•	•				
Weight		•				
Calculation of BSA		•				
Clinical Exam (to include neurological examination, skin and vital signs)[a]	•	•	As clinically indicated		•	•
Assessment for active infection[b]	•					
Pregnancy Test[c]	•[c]	•				
Haematology[d]	•	•	Day 8 and then as clinically indicated			
Blood Biochemistry[e]	•	•	Day 8 and then as clinically indicated			
Amylase and/or Lipase	•	•				
Thyroid Function Tests (to include TSH and T4 +/- FT3	•	•				
FSH[q]	•					
Coagulation: aPTT, PT/INR	•	•[p]	•[p]			
Urinalysis: dipstick	•	•	As clinically indicated			
ECG	•	As clinically indicated	As clinically indicated		•	

Imaging of tumour site(s) [f]	• Within 14 days			After C2, 4, 6 and 8 and then no later than every 3 cycles [g]	•	
RECIST1.1 reporting of imaging	•			After each imaging assessment		
CT Chest[h]	•			After C2, 4, 6 and 8 and then no later than every 3 cycles [g]		
Chest X-ray [h] *(if CT chest –ve)*	•			As clinically indicated	•	
Hand/wrist x-ray [i]	•					•[j]
Dental panorama x-ray [i]	•[i]					•[j]
Staging as per local practice[k,l]	•	As per local practice				
Tumour Biopsy *(as standard of care)*[m]	•					
Fresh frozen tumour if biopsy undertaken *(as standard of care)*	•					
BM Aspirate/trephine biopsy *(as standard of care)*	•			Repeat if clinically indicated		
Quality of Life Questionnaire (PedsQL/EORTC)	•			On Day 1 of cycle 3 and 5		
Taste and palatability questionnaire [n]			Day 8 of cycle 1 or Day 1 of cycle 2			
Blood Sample for Pharmacokinetics[o]			Cycles 1 See section 11.4.1.1for further details.			
Exploratory biological studies	See section 11.4.1.2					
FFPE for biomarker assessment	From any available surgery (e.g. diagnosis and any subsequent relapse)					
Adverse Event Reporting	Throughout the entire treatment phase and 30 days after end of treatment					
Concomitant medication reporting	Throughout the entire treatment phase					
Drug Accountability	Throughout the entire treatment phase					
CRF Completion	Throughout trial duration					

a. To include temperature, blood pressure, heart rate, respiratory rate
b. Assessment to include testing for Hepatitis B and C and HIV in patients with deranged liver function and/or HIV if clinically indicated
c. A highly sensitive test: for female patients of child bearing potential only. Screening pregnancy test to be carried out within 7 days of treatment planned randomisation. Does not require repeat if conducted within 3 days of first cycle. Ongoing pregnancy tests are required during treatment, recommended prior to each subsequent cycle.

d. To include at screening: haemoglobin, haematocrit, platelets and whole blood count with differentials. To include haemoglobin platelets and whole blood count with differentials. prior to each cycle. Evaluation prior to first dose does not need to be repeated if screening assessment within 3 days of first cycle.

e. To include at screening: AST/ALT, total bilirubin, ALP, creatinine, potassium, sodium, total calcium, magnesium, phosphate, and where possible albumin, glucose, direct bilirubin, uric acid, and urea/BUN. To include AST/ALT, total bilirubin prior to each cycle. Evaluation prior to first dose does not need to be repeated if screening assessment within 3 days of first cycle.

ALT and/or AST acceptable for routine monitoring purposes. Where liver damage is suspected, both tests are required

f. For patients with soft tissue disease: MRI is recommended including DW-MRI where possible Use same mode of investigation (MRI or CT) of tumour sites throughout study. On suspicion of Progressive Disease (PD) every effort should be made to obtain radiological confirmation of PD). Note: In cases where radiographic evaluation is not possible, clinical progression may be used.

g. To be performed prior to start of next cycle, ideally within 7 days of start of next cycle.

h. In patients with pulmonary/pleural metastatic disease, a CT scan of the chest should be performed to assess response or progression. Follow guidelines for imaging tumour sites

Patients with no evidence of pulmonary/pleural metastatic disease on baseline CT scan can be followed with chest x-ray.

i. Within 7 days of starting treatment. Patients < 18 years of age. At least annual while on treatment. All hand/wrist X-rays will be performed until the patient has reached the maximal skeletal age of the Greulich and Pyle standard (18 years for females and 19 years for males).

j. If received 6 or more cycles of treatment and not fully grown out at baseline. At least annual for 2 years

k. Staging as per local practice; FDG PET CT is investigation of choice, otherwise as per local practice; use same mode of investigation throughout study. Bilateral bone marrow aspirate and trephine biopsy recommended

l. In patients with metastatic disease detected by FDG-PET CT a follow up scan should be performed to assess response prior to local therapy.

m. Strongly encouraged

n. Patient receiving regorafenib

o. All patients at selected sites, see 3.1

p. Monitoring required in patients with conditions predisposing to bleeding, and in those treated with anticoagulants (e.g. warfarin and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding.

q. Where required nationally to confirm if participant is of child bearing potential.

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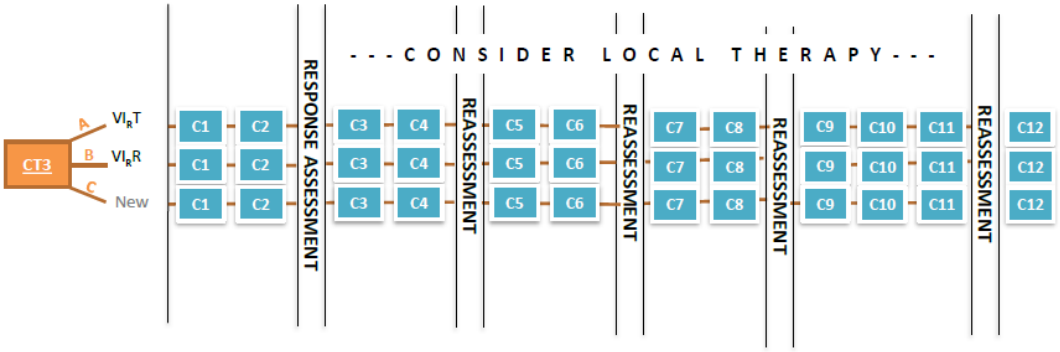
11.2 CT3 Relapsed Chemotherapy

Patients with relapsed disease will be randomised to receive either o VI_RT (Vincristine, Irinotecan, Temozolomide) or VI_RR (Vincristine, Irinotecan, Regorafenib)

The MAMS trial design will allow new agents to be investigated in the future.

Figure 9: CT3 Relapsed chemotherapy schema



11.2.1 Inclusion

1. Entered in to the FaR-RMS study (at diagnosis or at any subsequent time point)
2. First or subsequent relapse of histologically verified RMS
3. Age ≥ 6 months
4. Measurable or evaluable disease
5. No cytotoxic chemotherapy or other investigational medicinal product (IMP) within previous three weeks: within two weeks for vinorelbine and cyclophosphamide maintenance chemotherapy
6. Medically fit to receive trial treatment
7. Documented negative pregnancy test for female patients of childbearing potential within 7 days of planned randomisation
8. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active
9. Written informed consent from the patient and/or the parent/legal guardian

11.2.2 Exclusion

1. Progression during frontline therapy without previous response (=Refractory to first line treatment)
2. Prior regorafenib or temozolomide
3. Active > grade 1 diarrhoea
4. ALT or AST >3.0 x upper limit normal (ULN)
5. Bilirubin, Total >1.5 x ULN; total bilirubin is allowed up to 3 x ULN if Gilbert's syndrome is documented
6. Patients with unstable angina or new onset angina (within 3 months of planned date of randomisation), recent myocardial infarction (within 6 months of randomisation) and those with cardiac failure New York Heart Association (NYHA) Classification 2 or higher
   Cardiac abnormalities such as congestive heart failure (Modified Ross Heart Failure Classification for Children = class 2) and cardiac arrhythmias requiring antiarrhythmic therapy (beta blockers or digoxin are permitted)
7. Uncontrolled hypertension ≥ 95th centile for age and gender
8. Prior allo- or autologous Stem Cell Transplant
9. Uncontrolled inter-current illness or active infection
10. Pre-existing medical condition precluding treatment
11. Known hypersensitivity to any of the treatments or excipients
12. Second malignancy
13. Pregnant or breastfeeding women

11.2.3 Assessments

See Table 7: Schedule of Assessments for relapsed patients

11.2.4 CT3 Treatment Schedules

Cycles of chemotherapy will be given at 21 day intervals providing there is evidence of haematological recovery to ANC ≥1.0 x 10^9/L, platelets ≥80 x 10^9/L and diarrhoea resolved to grade 1 or less.

Please see APPENDIX 1.vi for further details.

Baseline liver function tests should be done before starting temozolomide or regorafenib treatment. If these tests are abnormal, physicians should consider the balance of benefits and risks when deciding whether to start treatment.

BSA to be calculated using the Mosteller formula

VI_RT	**21 day intervals. Up to 12 cycles**		
Vincristine	Days 1 & 8.	1.5mg/m^2	As per local practice, recommended as a short infusion Maximum dose: 2mg.
Irinotecan	Days 1,2,3,4&5	50mg/m2	As an i.v infusion over 1 hour
Temozolomide	Days 1,2,3,4&5	125mg/m2	Oral. Prior to vincristine and irinotecan. Escalate to 150mg/m2/day in Cycle 2 if no toxicity > grade 3
Cefixime* or equivalent	Day -2 to Day +7	8mg/kg once daily by mouth	Recommended (but not mandated) for prophylaxis of irinotecan-induced diarrhoea. Maximum dose: 400mg

Temozolomide: The starting dose will be 125 mg/m²/day. The dose of will be escalated to 150 mg/m²/day at cycle 2 for patients who do not experience ≥ grade 3 toxicity of any kind. The dose should be rounded to the nearest 5 mg.

Temozolomide will be given orally, on an empty stomach, **prior to vincristine and irinotecan**, on days 1-5, repeated every 3-weeks. If the patient vomits within 20 minutes of taking a dose, the dose should be re-administered.

The capsules must be swallowed whole with a glass of water. For young children and patients who have difficulty swallowing capsules, the full daily dose capsules should be placed in 10-30 ml of fruit juice or compote and administered after the capsules have been allowed to soften for 15-20 minutes or according to standard local practice.

BSA to be calculated using the Mosteller formula

VI_RR	21 day intervals. Up to 12 cycles		
Vincristine	Days 1 & 8.	1.5mg/m^2 See APPENDIX 3 and APPENDIX 4	As per local practice, recommended as a short infusion Maximum dose: 2mg.
Irinotecan	Days 1,2,3,4 & 5	50mg/m^2	As an i.v infusion over 1 hour
Regorafenib	Days 8 to 21	**Fixed dose of 120 mg for patients over 12 years of age AND ≥ 40 kg** For children less than 12 and/or less than 40kg dose = 82 mg/m^2 Maximum 120 mg For children between 6 and 24 months = 65 mg/m^2	Oral
Cefixime* or equivalent	Day -2 to Day +7	8mg/kg once daily by mouth	Recommended (but not mandated) for prophylaxis of irinotecan-induced diarrhoea. Maximum dose: 400 mg

Regorafenib may be taken as a tablet (only for patients with surface area of 0,86m2 or above) or in granule form (all patients). Dose modifications for younger/smaller children and toxicity are shown below (11.2.4.1 and 11.2.4.2).

Regorafenib should be taken in the morning approximately at the same time each day. The tablets should be swallowed whole with a glass of water after a light, low fat, meal.

Regorafenib granules will be administered mixed preferably in apple sauce or yogurt. In case apple sauce or yoghurt are not tolerated a low-fat alternative with similar consistency e.g. fruit puree may be used. Once mixed, the portion with the study drug must be eaten immediately. The content of the whole sachet must be used, i.e. one sachet must not be divided into smaller portions.

11.2.4.1 Regorafenib : dose modifications for toxicity

Starting dose	1st dose reduction (Dose Modification Level 1)	2nd dose reduction (Dose Modification Level 2)
120 mg	100 mg	80 mg

11.2.4.2 Regorafenib dose rounding /modifications for toxicity for younger/smaller children: less than 12 years and/or less than 40kg

Tablets:

BSA (m2)	Starting dose	1st dose reduction (Dose Modification Level 1)	2nd dose reduction (Dose Modification Level 2)
	82 mg/m2	**72 mg/m2**	**60 mg/m2**
< 0.86	Please use granules		
0.86-1.03	80 mg	60 mg	40 mg
1.04-1.34	100 mg	80 mg	60 mg
1.35-up	120 mg	100 mg	80 mg

Granules:

BSA (m2)	Starting dose	1st dose reduction (Dose Modification Level 1)	2nd dose reduction (Dose Modification Level 2)
	82 mg/m2	**72 mg/m2**	**60 mg/m2**
0.41-0.45	35 mg	30 mg	25mg
0.46-0.51	40 mg	35 mg	30 mg
0.52-0.57	45 mg	40 mg	35 mg
0.58-0.63	50 mg	45 mg	40 mg
0.64-0.70	55 mg	50 mg	40 mg
0.71-0.76	60 mg	55 mg	45 mg
0.77-0.81	65 mg	60 mg	50 mg

0.82-.0.87	70 mg	60 mg	50 mg
0.88-0.93	75 mg	65 mg	55 mg
0.94-1.03	80 mg	75 mg	60 mg
1.04-1.15	90 mg	80 mg	70 mg
1.16-1.28	100 mg	90 mg	75 mg
1.29-1.40	110 mg	100 mg	80 mg
1.41- up	120 mg	100 mg	80 mg

Dosing of regorafenib granulates based on BSA for children from 6 to less than 24 months old			
BSA (m^2)	**Starting dose**	**1st dose reduction (Dose Modification Level 1)**	**2nd dose reduction (Dose Modification Level 2)**
	65 mg/m^2	60 mg/m^2	45 mg/m^2
0.29 - 0.35	20 mg	15 mg	10 mg
0.36 – 0.42	25 mg	20 mg	15 mg
0.43 – 0.49	30 mg	25 mg	20 mg
0.50 – 0.61	35 mg	30 mg	25 mg
0.62 – 0.71	45 mg	40 mg	30 mg
0.72 – 0.80	50 mg	45 mg	35 mg

11.2.5 Duration of treatment

In the absence of disease progression, up to 12 cycles of treatment may be given. Treatment beyond 12 cycles should be discussed with a Clinical Coordinator.

11.2.6 CT3 Dose Modifications

Regorafenib should be permanently discontinued in the event of:

- Severe bleeding necessitating urgent medical intervention
- Gastrointestinal perforation or fistula
- Hypertensive crisis
- Steven Johnson's syndrome
- Toxic epidermal necrolysis
- Posterior reversible encephalopathy syndrome (PRES)

See APPENDIX 3 and APPENDIX 4 for dose modifications for smaller/younger patients

See section 12 for other dose modifications due to toxicity.

11.2.7 CT3 Prohibited Medications

See section 13 for warnings and section 15 for a list of prohibited concomitant medications

11.3 Timing of local control in relapse

Patients for whom local therapy (surgery and/or radiotherapy) to relapsed disease site(s) is feasible are strongly encouraged to receive appropriate local therapy as decided by the treating clinician after 2 or more cycles of chemotherapy.

It is expected that VI_RT or VI_RR will be compatible with radiotherapy but this should be discussed with the responsible clinical oncologist.

Where local therapy options are feasible, a mutilating operation may be justified, particularly if radiotherapy options have already been exhausted [82]. A palliative procedure may also be considered where it is likely to improve quality of life.

See EpSSG Surgical Guidelines for further information (see APPENDIX 14).

11.3.1 Surgery (patients receiving regorafenib):

Major surgery should only be performed during the study period if, in the opinion of the investigator and after careful individual benefit/risk assessment (taking into account the benefits outweigh the risks. Wound healing complications that have been described with all anti-VEGF drugs, so particular care should be taken in those patients randomised to receive regorafenib.
If surgery is deemed to be in the patient's best interests and the benefits outweigh the risks, regorafenib should be stopped at least 14 days prior to the scheduled major surgery. The decision to resume regorafenib after surgery should be based on clinical judgment of adequate wound healing.

See EpSSG Surgical Guidelines for further information. See APPENDIX 14.

11.3.2 Radiotherapy:

Concomitant radiation therapy with systemic therapy is allowed and regorafenib may be continued during radiotherapy after an individual benefit-risk assessment.

11.4 Exploratory Biological Biomarker Parameters

Assessment of biomarkers in tumour samples (at relapse and/or diagnosis) and blood samples where available, and whenever possible, will be undertaken. The biomarker analysis may include, but not limited to the following, as sample availability allows: From tumour tissue: whole exome sequencing (WES)/Next generation panel sequencing (NGS); 3'mRNA sequencing; RNA fusion panel testing. From whole blood: germline sequencing. From serial blood plasma samples: circulating tumour (ct) DNA analysis. From serum samples: measurement of soluble biomarkers (e.g. sVEGFR2, VWF, etc.).

11.4.1 Biological Sample Collection

11.4.1.1 Pharmacokinetics (PK)

PK sampling will be performed at selected sites. Where feasible, every effort should be made to perform PK sampling for all patients receiving regorafenib at these sites.

As a minimum PK sampling must be completed in approximately 6 patients who are between 6 months to 2 years of age, approximately 6 patients who are >2 to 6 years of age, and in approximately 6 patients that are ≥12 to 18 years of age and ≥40kg, i.e. those who are receiving the 120 mg flat dose.

		Pharmacokinetic sampling schedule for regorafenib in cycle 1		
Sample	**Volume**	**Period**	**Treatment Cycle 1**	
		Day	Day 14 (or days 12-13, 15)	Day 21 (or days 19,20)
Whole blood for plasma PKs	1.2-2.5ml Minimum 1.2 ml	≥ 2 years	2-4 hours post dose	Pre-dose 2-4 hours post dose 5-8 hours post dose
Whole blood for plasma PKs	1.2-2.5ml Minimum 1.2 ml	6 to < 24 months	**N/A**	Pre-dose 2-8 hours post dose

11.4.1.2 Exploratory biological sample collection

From all patients (where consent provided).

See APPENDIX 21 for guidance on blood volumes for smaller children.

	Days from first dose **Samples must be taken pre dose on the day of treatment**					
Sample	Volume/tissue specification	Screening		End of treatment	At relapse /progression	Analysis
Whole blood in PAXgene® for germline analysis	Ideally 5-10 ml	✓ (or start of cycle 2)				Analysis WES:Germline
Whole blood for serum biomarkers (regorafenib arm only)	2 ml	within 7 days of starting treatment	pre-dose sample for cycle 2 Day 1 and cycle 3 Day 1.	✓		Bayer serum biomarker
Whole blood in EDTA tubes for ctDNA	5-10 ml	✓	Pre- dose on day 1 of cycles 2, 4, 6, 8 and then every 2-3 cycles at the same time as radiological assessment	✓	✓	CtDNA
Paraffin embedded tumour tissue	Paraffin block (for details see lab manual)	From any available surgery (e.g. diagnosis and any subsequent relapse)			3'mRNA sequencing, WES/NGS panel sequencing, Fusion-break point analysis	

11.4.2 Diffusion Weighted MRI Imaging

Diffusion-weighted Magnetic Resonance Imaging (MRI) alongside the standard assessment imaging is strongly encouraged in all patients in accordance with the EpSSG Imaging guidelines.

For DWI-MRI of the primary tumour the following 4 B-values should be used: 0, 100, 500 and 1000 s/mm^2. DWI should be performed in the axial plane. For scanner and site specific MR protocols see appendix DW-MRI guidelines. It is important to save all files in DICOM format, preferably including the raw DW-MRI data for future potential harmonization or re-processing with up-to-date algorithms.

For this imaging will be uploaded in a dedicated database onto the QUARTET platform.

Also, see APPENDIX 15.

12. CHEMOTHERAPY TOXICITY DOSE MODIFICATIONS

For regorafenib dose rounding following dose modification see section 11.2.4.1and 11.2.4.2

Haematological toxicity (all schedules except the phase 1B studies)

Preference should be given to G-CSF support rather than dose reduction or dose delay.

If significant toxicity continues despite G-CSF support as defined by:

Haematological recovery (ANC ≥1.0 x 10^9/L, platelets ≥80 x 10^9/L) delayed ≥14 days or ≥ 7 days for >2 cycles

Repeated episodes of grade 4 febrile neutropenia after ≥ 2 cycles:

- Then consider dose reduction of 20%-30% of the drugs likely to have caused myelosuppression

If toxicity persists discuss with a Clinical Coordinator.

Interstitial pneumonitis

Pneumonitis has been reported during and following treatment with cyclophosphamide and ifosfamide, although the risk of developing this is unknown. Please consult with a respiratory clinician if this event occurs.

Irinotecan induced toxicity

As part of the clinical management of irinotecan-induced toxicity, testing for UGT1A1 polymorphism is strongly recommended in patients with significant irinotecan-related haematological or gut toxicity.

Irinotecan related Diarrhoea

Irinotecan-associated diarrhoea may be characterised as ‘early onset’ or ‘late onset’.

‘Early onset’ diarrhoea occurs within 8 hours of the first irinotecan dose and may be associated with other cholinergic symptoms (Cholinergic syndrome).

- Give atropine according to institutional guidelines. Consider prophylactic atropine prior to subsequent irinotecan doses.

‘Late onset’ diarrhoea occurs 24 or more hours after irinotecan dose.

- Loperamide should be given according to institutional guidelines. Patients and/or parents/carers should be counselled as to the need to start loperamide promptly once diarrhoea has started and seek further advice from their treatment centre if diarrhoea is uncontrolled with maximal loperamide dosing.
- Consider prophylactic cefixime or equivalent 8 mg/kg (under 12 years) or 400 mg (over 12 years) daily by mouth from d 6 to d 14 (days -2 to day +7 in relapse) if not already given.

Grade ≥3 diarrhoea for more than 3 days despite maximum loperamide therapy:

- Consider the use of other supportive care measures following discussion with local gastrointestinal team
- Reduce irinotecan dose by 20-30% for next cycle
- If diarrhoea is ongoing on day 21, delay next cycle for up to 2 weeks (loperamide allowed) until diarrhoea resolves to ≤ grade 1

- If grade 3 or 4 toxicity persists >2 weeks despite suitable symptomatic treatment, consider discontinuation of study treatment

If grade ≥3 diarrhoea occurs with a reduced dose of irinotecan:

- Reduce irinotecan dose by another 20-30%% for next cycle
- If diarrhoea is ongoing on day 21 (loperamide allowed), delay next cycle for up to 2 weeks until diarrhoea resolves to ≤ grade 1
- If diarrhoea > grade 1 persists >2 weeks despite suitable symptomatic treatment, consider discontinuation of irinotecan (for patients receiving I_RIVA) or discontinuation of study treatment (VI_RT or VI_RR).

Nephrotoxicity / Renal function monitoring

Serum creatinine should be monitored prior to each cycle of ifosfamide

Glomerular Filtration Rate (GFR) should be assessed according to institutional practice.

Tubular function should be monitored as per institutional practice prior to each cycle containing Ifosfamide.

Ifosfamide adjustment to renal function

If measured or estimated GFR falls <60ml/min/1.73m^2 or if the tubular reabsorption of phosphate (tubular maximum reabsorption of phosphate (Tmp)/GFR) falls to <0.8 mmol/L it is strongly recommended to discontinue ifosfamide and substitute with cyclophosphamide at a dose of 1500 mg/m² per course for the remaining courses of treatment.

A dose reduction of ifosfamide of 20-30% may also be considered if a steady fall in GFR or tubular reabsorption of phosphate is occurring. Please refer to local institutional practice.

Central neurotoxicity

If central neurotoxicity occurs stop ifosfamide immediately and treat with methylthioninium chloride (methylene blue).

For Grade 1-2 central neurotoxicity consider methylene blue prophylaxis and re-challenge with ifosfamide at full dose.

For Grade 3 or 4 central neurotoxicity, discontinue ifosfamide permanently and substitute with cyclophosphamide 1500 mg/m^2/course

Cardiotoxicity

In this protocol the total cumulative dose of doxorubicin is 240 mg/m^2, therefore lower than the threshold dose for late cardiotoxicity reported in most studies. However, careful monitoring for possible acute or late cardiotoxicity is recommended.

Significant deterioration in cardiac function is indicated by a shortening fraction (SF) <28%. In this event, temporarily withdraw doxorubicin

A fall in shortening fraction by an absolute value of >10 percentile units but with an actual SF value >28% (i.e. from SF 42% to SF 31%) may also represent a significant deterioration in function. In this event omit doxorubicin in the next course.

If the decrease is not persistently proven, i.e. if repeated investigations (after a week) cannot reproduce the dysfunction, doxorubicin can be recommenced.

If persistent deterioration of myocardial function occurs, e.g. persistent decrease in fractional shortening by an absolute value of 10 percentile points from previous tests or a persistent fractional shortening below 28%, consider avoiding further doxorubicin and refer the patient to a cardiologist.

Other cardiac toxicity should be managed as per 'Other grade 3 or 4 non-haematological toxicities'.

Veno-occlusive disease (VOD)

A particular type of hepatic toxicity is veno-occlusive disease (VOD) which appears to be related to the administration of various drugs, particularly Actinomycin D. No specific predisposing factor has been found to identify the patient at risk, but young children and infants have highest risk of development [22]. A prior persistent or slow recovery of thrombocytopenia may be an indicator of VOD. In case of VOD, the suspect drug(s) should not be given until the liver dysfunction has returned to normal. Centres should follow institutional guidelines for management of patients with a diagnosis of VOD.

The first dose after recommencing the suspect drug(s) should be at 50% of the previous dose. If tolerated may be increased progressively in the following cycles.

If the symptoms re-appear the suspect drug(s) should be withdrawn permanently.

Other hepatic toxicity should be managed as per 'Other grade 3 or 4 non-haematological toxicities'.

Regorafenib related Hand-foot skin reaction (HFSR, Palmar plantar erythrodysesthesia syndrome)

Grade 1 HFSR should be managed using supportive measures and symptomatic relief according to institutional practice; maintaining dose.

Grade 2 HFSR:

- Manage using supportive measures and symptomatic relief according to institutional practice
- Reduce regorafenib dose by one dose modification level for next cycle
- If ongoing after 7 days, interrupt regorafenib until resolves to ≤ grade 1
- If reoccurs, interrupt regorafenib until resolves to ≤ grade 1, reduce subsequent dose by one dose modification level
- If toxicity recurs more than 3 times; discontinue regorafenib

Grade 3 HFSR:

- Manage using supportive measures and symptomatic relief according to institutional practice
- Interrupt regorafenib until resolves to ≤ grade 1
- Reduce subsequent dose by one dose modification level
- If reoccurs, interrupt regorafenib until resolves to ≤ grade 1, reduce subsequent dose by one dose modification level
- If toxicity recurs more than twice; discontinue regorafenib

Regorafenib related Stevens Johnson Syndrome/Toxic Epidermal Necrolysis

If Stevens Johnson Syndrome or toxic epidermal necrolysis occurs, regorafenib must be stopped permanently. Re-challenge with regorafenib is not permitted.

Regorafenib related hypertension

Antihypertensive medication is allowed. The selection of anti-hypertensive medication used in this setting should be performed at the investigator's discretion, considering possible site-specific treatment guideline

Grade 2

- If symptomatic, withhold regorafenib until symptoms resolve and Blood Pressure ≤95th percentile for age and gender (table). Restart at same dose

Grade 3

- Withhold regorafenib until Blood Pressure ≤95th percentile for age and gender and if symptomatic, until symptoms resolve. Restart at same dose
- If uncontrolled then reduce subsequent dose by one dose modification level
- If recurs despite dose reduction and antihypertensive therapy, reduce subsequent dose by one dose modification level

Grade 4 – discontinue regorafenib

Regorafenib related hepatotoxicity

Dose modifications for observed elevations of ALT and/or AST

- Grade 2 (Maximum)- ≤5 times upper limit of normal (ULN) Continue treatment and monitor Liver function weekly until transaminases return to <3 times ULN or baseline

Grade 3>5 times ULN ≤20 times ULN

- 1st occurrence- Interrupt Regorafenib treatment and monitor transaminases weekly until return to <3 times ULN or baseline*

*Restart: If the potential benefit outweighs the risk of hepatotoxicity, re-start Regorafenib treatment, reduce dose by one dose level and monitor liver function weekly for at least 4 weeks

- Re-occurrence- Discontinue Regorafenib treatment permanently

Grade 4 - >20 times ULN

- - Discontinue Regorafenib treatment permanently

Grade 2 (or higher) > 3 times ULN with concurrent bilirubin >2 times ULN

- Discontinue Regorafenib treatment permanently, monitor liver function weekly until resolution or return to baseline
- **Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.**

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES has been reported in association with regorafenib treatment. Signs and symptoms of PRES include seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging. PRES occurring in association with regorafenib should be managed with supportive measures and regorafenib must be permanently discontinued.

Other grade 3 or 4 non-haematological toxicities

Investigators may use their discretion with regards to dose reductions. In general, however, for other grade 3 or 4 non-haematological toxicities attributed to study treatment:

- Withhold suspect drug until toxicity resolves to ≤ grade 2
- If toxicity has resolved to ≤ grade 2 by day 35, agents may be restarted with a 20% - 30% dose (for regorafenib one dose modification level) reduction of the responsible agent.

Grade 3 or 4 non-haematological toxicity after one dose reduction:

- a second 20%-30% (for regorafenib one dose modification level) dose reduction may be made

Grade 3 or 4 non-haematological toxicity after two dose reductions:

- If toxicity persists then contact a Clinical Coordinator

13. WARNINGS

Toxicity may be enhanced during chemotherapy in combination with radiotherapy. Investigators are advised that extra vigilance is required during this time.

Vincristine and vinorelbine are vinca alkaloids and reference should be made to institutional guidelines with respect to the route of administration of vinca alkaloids.

Co-administration with neomycin may result in a decreased efficacy of regorafenib

Acute respiratory distress syndrome (ARDS) has been reported with vinorelbine.

14. SUPPORTIVE CARE

Anti-emetics

Patients should be treated with appropriate anti-emetics according to institutional guidelines.

Blood products

Blood and platelet transfusions and the use of filtered or irradiated blood products should follow local institutional guidelines.

Constipation prophylaxis

The use of constipation prophylaxis should follow institutional guidelines.

Dexrazoxane

Dexrazoxane is a permissive supportive care treatment to be used alongside doxorubicin

Diarrhoeal prophylaxis

Systematic treatment with oral cefixime or equivalent is recommended for all patients receiving irinotecan and will be given for 9 days in total starting 2 days before irinotecan (D 6 to D 14; day -2 to day +7 in relapse). For cefixime, 8 mg/kg once a day (maximum daily dose 400 mg).

Granulocyte colony-stimulating factor

G-CSF support is not routinely recommended but is preferable to dose reduction or dose delay for all regimens. G-CSF administration should follow institutional guidelines and must be stopped 48 hours prior to chemotherapy commencing. G-CSF is not permitted during the dose determining phase of phase Ib components.

Neutropenic fever

The use of antibiotics and the use of G-CSF should follow institutional guidelines.

Pneumocystis jirovecii infection prophylaxis

Pneumocystis jirovecii prophylaxis should be given according to institutional guidelines.

Preservation of fertility

Risks of infertility and premature ovarian failure are increased following treatment with any alkylating therapy. Post-pubertal males are routinely given the opportunity to cryopreserve sperm prior to treatment. Post-pubertal females may be offered fertility preservation by cryopreservation of eggs or ovarian tissue according to local institutional practice. Other options for cryopreservation for prepubertal patients may be available and should be offered according to institutional practice.

At relapse: Risks of infertility and premature ovarian failure are increased following treatment with any alkylating therapy. Post-pubertal males are routinely given the opportunity to cryopreserve sperm prior to treatment.The risks of regorafenib to fertility are unknown. Consideration should be given as to the relevance of fertility preservation according to the clinical situation, if not already performed before first line treatment. Post-pubertal males are routinely given the opportunity to cryopreserve sperm prior to treatment. Post-pubertal females may be offered fertility preservation by cryopreservation of eggs or ovarian tissue according to local institutional practice. Other options for cryopreservation for prepubertal patients may be available and should be offered according to institutional practice and clinical relevance in the relapse setting.

However, men must refrain from donating sperm for 6 months after receiving the last dose of study treatment.

Tumour Lysis Syndrome

In rare circumstances where patients have a heavy tumour burden, Tumour Lysis may occur. Management of Tumour Lysis will be according to institutional guidelines.

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Acute respiratory distress syndrome (ARDS) with vinorelbine:

Refer to the SmPC for vinorelbine and ensure that the guidance regarding ARDS is followed.

Hereditary Fructose Intolerance:

Ensure that reference to the SmPC for irinotecan and vinorelbine is made and ensure that the guidance regarding hereditary fructose intolerance is followed.

15. PROHIBITED CONCOMITANT MEDICATION

The use of specific drugs which may interact with the trial IMPs must be avoided. A full list of drugs to avoid can be found in the Summary of Product Characteristics. However, of note:

- Anti-cancer treatment as part of another interventional research protocol.
- Inhibitors and inducers of CYP3A4 , CYP2D6 and P-glycoprotein should be avoided where contraindicated in the SmPC, e.g. rifampicin, voriconazole, Itraconazole, ketoconazole.
- Strong inhibitors of UGT1A9 should be avoided in patients taking regorafenib.

- Any homeopathic or other agent delivered with anti-tumour intent is prohibited.
- Live vaccines are prohibited during treatment and up to 6 months following the last study treatment.
- Some anticonvulsants may be contraindicated, e.g. carbamazepine, phenytoin, phenobarbital.
- Food or beverages containing grapefruit should be avoided during treatment period with regorafenib.
- The use of breast cancer resistance protein (BCRP) substrates should be used with caution in patients taking regorafenib.

In CT3 (relapse) all concomitant medications will be recorded

In all other treatment questions: concomitant medications will be recorded as part of Serious Adverse Event (SAE) reporting only. Where concomitant medications are given in relation to standard clinical management, this information will not be recorded in the CRF.

16. RADIOTHERAPY

This section should be read in conjunction with the current version of the FaR-RMS QUARTET Radiotherapy Quality Assurance Guidelines.

16.1 Timing of local therapy

The decision to proceed to local therapy (surgery and/or radiotherapy) should be made after 3 cycles of induction chemotherapy (or after 6 cycles for patients with metastatic disease). Where a patient is deemed suitable for radiotherapy, radiotherapy randomisations should be considered, as patients may be eligible to enter multiple radiotherapy questions.

The Union for International Cancer Control (UICC), which describes the absence or presence of residual tumour after treatment by the symbol R, will be used to express the quality of surgery. The R categories are: R0 = no residual tumour, R1 = microscopic residual tumour, and R2 = macroscopic residual tumour [83].

Where a patient is not eligible for or chooses not to take part in the radiotherapy randomisations patients should be treated in accordance with local practice, the FaR-RMS QUARTET Radiotherapy Quality Assurance Guidelines may be referred to.

Preoperative, or definitive, radiotherapy for localised disease should be delivered after 4th cycle of chemotherapy (week 13), or after 7th cycle of chemotherapy for metastatic disease (week 22), with surgery then 4- 6 weeks after completion of radiotherapy.

Postoperative radiotherapy should commence with the 2nd cycle of postoperative chemotherapy, surgery having taken place at after 4th cycle of chemotherapy (week 13), or after 7th cycle of chemotherapy for metastatic disease (week 22).

Indications for radiotherapy

Radiotherapy to the site of the primary tumour is indicated for the majority patients, particularly those in the HR and VHR Groups; and the majority of Standard Risk Patients (Group C only).

Key exceptions which do not require radiotherapy are:

- Localised fusion negative rhabdomyosarcoma with initial R0 resection (IRS Group I) i.e. subgroups A and B
- Localised fusion negative rhabdomyosarcoma of the vagina achieving complete remission with induction chemotherapy
- A highly selected group of patients with IRS Group II/ III Standard Risk fusion negative RMS, arising at a favourable site, where secondary surgery achieves an R0 resection (e.g. paratesticular, uterus) i.e. subgroup C

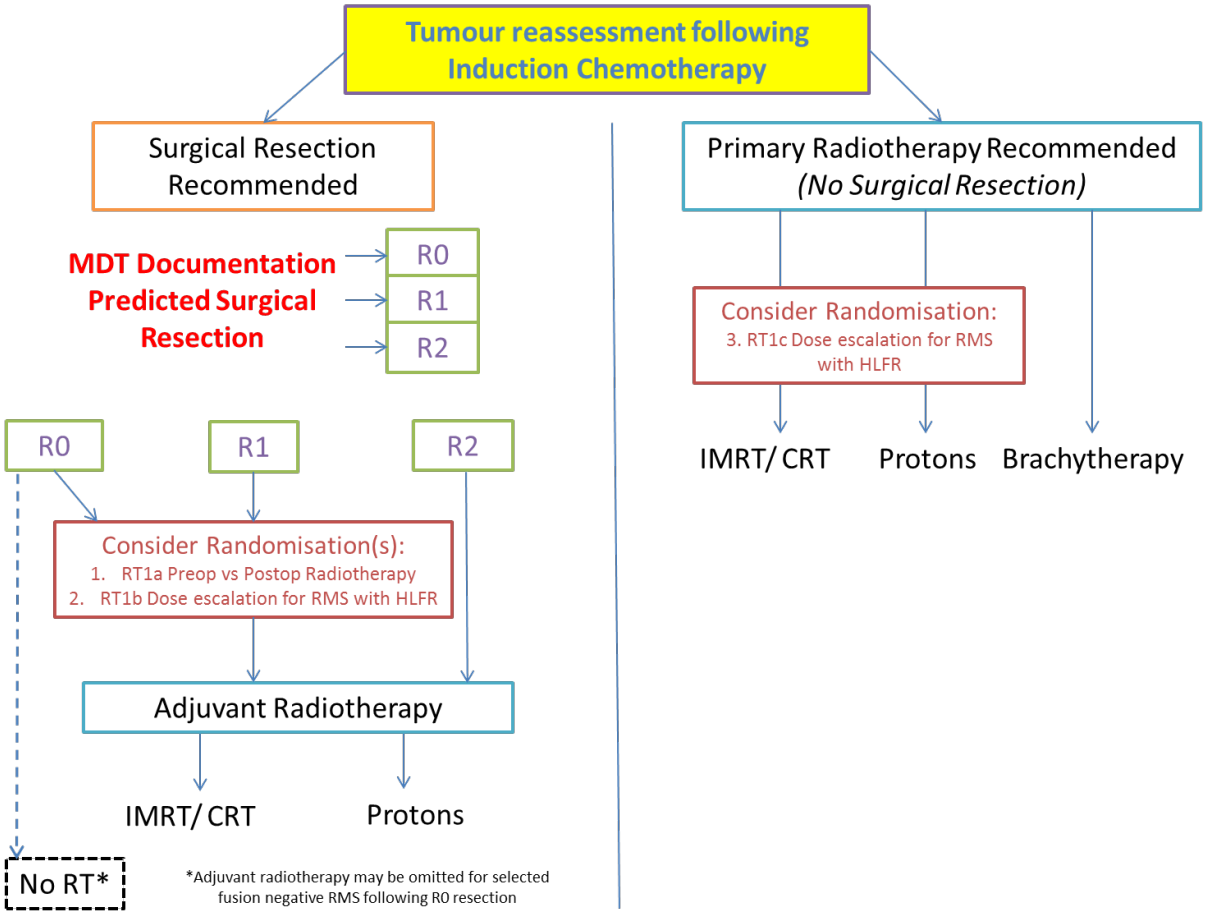
Note patients in subgroup C with IRS Group II/ III Standard Risk fusion negative RMS, at other favourable sites are likely to require radiotherapy (and may be eligible for the radiotherapy randomisation) e.g. bladder/ prostate; head and neck RMS, orbit, biliary.

Nodal disease: Radiotherapy should be delivered to all regional nodal sites involved at the time of presentation, irrespective of any additional surgical resection.

Metastatic disease: Radiotherapy should be delivered to all sites of metastatic disease that can feasibly be treated, unless patient being treated in the metastatic radiotherapy randomisation.

Children <2 years of age will not be eligible for the radiotherapy randomisations. Adherence to the FaR-RMS QUARTET Radiotherapy Quality Assurance Guidelines is encouraged; however, the decision to proceed with radiotherapy is at the discretion of the treating clinicians, considering tumour histology, tumour site, response to chemotherapy, and the potential late morbidity of local therapy.

Figure 10: Radiotherapy schema based on local therapy decision



16.2 Eligibility for radiotherapy randomisations

Where adjuvant radiotherapy to the primary tumour is indicated in addition to surgical resection, patients may be randomised to receive radiotherapy either pre or post operatively (RT1^{A}).

For patients with a higher local failure risk (HLFR) there will be further randomisations to receive either standard dose radiotherapy 41.4Gy versus dose escalated radiotherapy 50.4Gy (RT1^{B}) , with the additional 9Gy for dose escalated patients delivered to the extent of tumour remaining after 3 cycles of induction chemotherapy. Please see section RT1B Specific Inclusion16.2.2.2 for definition of HLFR.

Patients with standard Local Failure Risk (SLFR) will receive 41.4Gy, which is the standard dose for all patients receiving adjuvant radiotherapy in addition to surgery achieving an R0 or R1 resection.

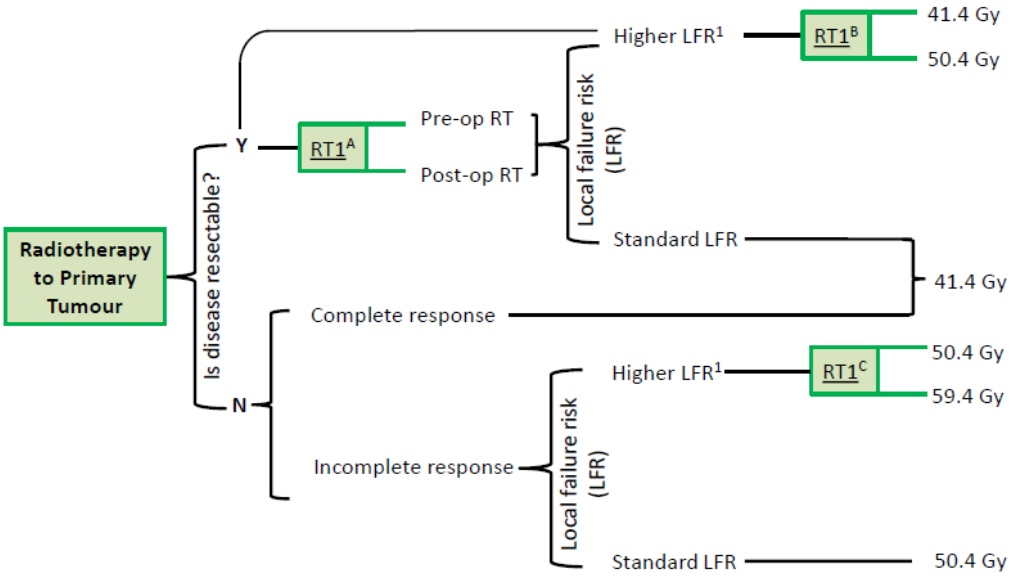
Patients with unresectable disease with a complete response following induction therapy will not be eligible to enter a radiotherapy trial question. They should be treated with standard dose radiotherapy for microscopic disease and receive 41.4Gy.

For patients whose tumour is not suitable for surgical resection, with an incomplete response following induction therapy, and where there is a HLFR, may be randomised between standard dose radiotherapy 50.4Gy versus dose escalated radiotherapy 59.4Gy (RT1C). For both arms 41.4Gy will be delivered to the extent of tumour at diagnosis, with the additional 9Gy (standard) or 18 Gy (dose escalated) delivered to the extent of tumour remaining after 3 cycles of induction chemotherapy. Please see section RT1C Specific Inclusion for definition of HLFR.

SLFR patients, and patients where surgery has only achieved an R2 resection will be treated with standard dose radiotherapy for macroscopic disease receiving 50.4Gy as described above. This is the standard dose for all patients receiving definitive radiotherapy treatment. These patients will not be eligible to enter a radiotherapy trial question, unless they also have unfavourable metastatic disease.

Note: eligible patients may enter multiple radiotherapy randomisations.

Figure 11: Radiotherapy to the primary tumour schema



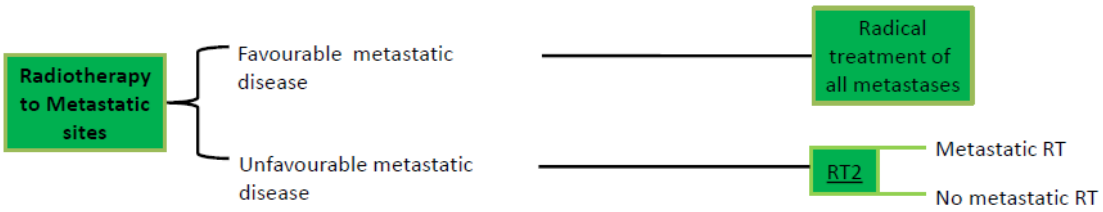
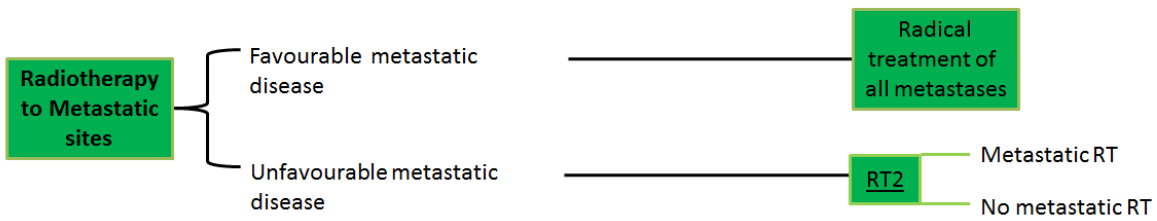


Figure 12: Radiotherapy to metastatic sites



16.2.1 Radiotherapy Inclusion – for all radiotherapy randomisations

1. Entered in to the FaR-RMS study (at diagnosis or prior to radiotherapy randomisation)
2. VHR, HR and SR disease (Subgroups C-H)
   - ≥ 2 years of age
3. Receiving frontline induction treatment as part of the FaR-RMS trial or with a IVA/IVADo based chemotherapy regimen, Note that, patients for whom ifosfamide has been replaced with cyclophosphamide will be eligible
4. Patient assessed as medically fit to receive the radiotherapy
5. Documented negative pregnancy test for female patients of childbearing potential
6. Patient agrees to use contraception during therapy and for 12 months after last trial treatment (females) or 6 months after last trial treatment (males), where patient is sexually active
7. Written informed consent from the patient and/or the parent/legal guardian

16.2.2 Radiotherapy Exclusion – for all radiotherapy randomisations

1. Prior allo- or autologous Stem Cell Transplant
2. Second malignancy
3. Pregnant or breastfeeding women
4. Receiving radiotherapy as brachytherapy

16.2.2.1 RT1^{A} Specific Inclusion

1. Primary tumour deemed resectable (predicted R0/ R1 resection) after 3 cycles of induction chemotherapy [2] (6 cycles for metastatic disease).
2. Adjuvant radiotherapy required in addition to delayed surgical resection of the primary tumour (local decision)
3. Available for randomisation after cycle 3 and prior to the start of cycle 5 of induction chemotherapy for localised disease, or after cycle 6 and prior to the start of cycle 8 for metastatic disease

16.2.2.2 RT1^{B} Specific Inclusion

1. Primary tumour deemed resectable (predicted R0/R1 resection) after 3 cycles of induction chemotherapy[1] (6 cycles for metastatic disease).
2. Adjuvant radiotherapy required in addition to surgical resection (local decision)
3. HLFR based on presence of either of the following criteria:
   a. Unfavourable site*
   b. Age ≥ 18yrs
4. Available for randomisation after cycle 3 and prior to the start of cycle 6 of induction chemotherapy for localised disease, or after cycle 6 and prior to the start of cycle 9 for metastatic disease

16.2.2.3 RT1^{C} Specific Inclusion

1. Definitive primary radiotherapy indicated (local decision)
2. HLFR based on either of the following criteria:
   a. Unfavourable site*
   b. Age ≥ 18yrs

[2] *In special cases where additional chemotherapy may facilitate complex surgical resection, clinicians may continue with 1-3 extra courses before taking the decision concerning local therapy,* ***however in general this is discouraged.***

3. Available for randomisation after cycle 3 and prior to the start of cycle 6 of induction chemotherapy for localised disease, or after cycle 6 and prior to the start of cycle 9 for metastatic disease

*Favourable sites are: GU including bladder-prostate, head & neck non-para meningeal, orbit and biliary primaries .

Unfavourable sites are: all other sites. See Appendix 18: DEFINITION OF SITES and APPENDIX 19 Regional lymph node definition

16.2.2.4 RT2

1. Available for randomisation after cycle 6 and before the start of cycle 9 of induction chemotherapy
2. Unfavourable metastatic disease, defined as Modified Oberlin Prognostic Score 2-4**

****Note: Definition of metastatic lesions for RT2 eligibility**

16.2.2.5 Modified Oberlin Prognostic Score (1 point for each adverse factor):

- Age ≥10y
- Extremity, Other, Unidentified Primary Site
- Bone and/ or Bone Marrow involvement
- ≥3 metastatic sites

Unfavourable metastatic disease: 2- 4 adverse factors

Favourable metastatic disease: 0-1 adverse factors

16.3 Assessments

See Table 6: Schedule of Assessments for new diagnosed frontline patient – Frontline Assessments. There are no specific radiotherapy assessments. Monitor patients as per standard practice including induction chemotherapy assessments.

16.4 Radiotherapy facilities and planning

16.4.1 Facility and equipment

Patients can receive radiotherapy treatment to the primary tumour using photon-based techniques (including IMRT), electrons or proton therapy/particle therapy. Patients can receive radiotherapy to metastatic sites using these same techniques, although other photon radiotherapy techniques including SBRT or SRT may also be used. A Simultaneous Integrated Boost (SIB) technique may be considered, and acceptable schedules are detailed in the FaR-RMS QUARTET Radiotherapy Quality Assurance Guidelines.

16.4.2 Patient position and data acquisition

Appropriate immobilization or motion mitigation strategies, depending on localization, are expected. All patients should be planned on a planning CT of appropriate slice thickness (typically 1- 3mm) with the aid all diagnostic and response assessment imaging available.

16.4.3 Definition of Radiotherapy Target Volumes & Margins

GTV

For radiotherapy treatment of the Primary Tumour Volume the Gross Tumour Volume (GTV) at presentation (GTVp_pre) will be delineated (or reconstructed) for all cases; this referring to the extent of disease at diagnosis, taking into account changes in anatomy and organ displacement resulting from chemotherapy related tumour shrinkage, or surgical resection.

For cases receiving definitive primary radiotherapy (including both arms of RT1^{C}), and those receiving adjuvant radiotherapy randomised to the dose escalation arm in RT1^{B}, an additional GTV will be defined based on the extent of the residual primary tumour on imaging obtained post induction chemotherapy (GTVp_post), taking into account changes in anatomy, and organ displacement, resulting from chemotherapy related tumour shrinkage, or surgical resection.

The nodal GTV (GTVn) should be delineated based on the gross extent of nodal involvement at diagnosis taking into account changes in anatomy and organ displacement resulting from chemotherapy related tumour shrinkage, or surgical resection. For exceptional cases with pathologically enlarged bulky macroscopic residual nodal disease post induction chemotherapy an additional boost should be delivered with this residual disease delineated as GTVn_post

CTV

Clinical Target Volumes (CTV) for the Primary tumour (CTVp) will be generated using the following margins:

- GTVp_pre to CTVp_pre: 1 cm
- For extremity primary tumour sites, superior and inferior CTV margins of 2 cm are required, with 1cm expansion circumferentially.
- Skin, scar, drain or biopsy sites should not be included in the CTVp, except in cases of involvement with gross tumour.
- GTVp_post to CTVp_post: 0.5 cm
- For tumours arising adjacent to body cavities (e.g. thorax, abdomen, pelvis) that extend or 'push' into the cavity but do not infiltrate adjacent organs or tissues, then the GTVp should only be expanded, by 1cm (GTVp_pre) or 0.5cm (GTVp_post), in the direction of potential infiltration, and there should be no extension of the CTVp into the adjacent, uninvolved body cavity.
- GTVn to CTVn: 3cm superiorly and inferiorly (or in direction of nodal drainage), and circumferentially to include adjacent lymph nodes in the anatomically constrained lymph node site. Wherever possible, displaced normal tissue should be excluded from the CTVn. In cases of uncertainty, or where particular concern, about exact extent of nodal involvement at diagnosis then an involved field concept should be used.
- For bulky residual involved lymph nodes, GTVn_post to CTVn_post: 0.5 cm

ITV

For primary tumour sites where respiratory-related motion needs to be considered (e.g. thorax, upper abdomen) the use of 4DCT and an Internal Target Volume (ITV) approach is allowed, based on local practice. This will be denoted as ITVp.

PTV

Expansion from the CTVs or ITVs to PTVs is to be undertaken as per local standard of care, based on the specific radiotherapy technique, image guidance strategy and set up errors, and is usually in the range of 3 to 10 mm.

16.5 Radiotherapy treatment to the primary tumour

16.5.1 Definition Dose Prescription and Dose Fractionation for primary tumour

- **Resectable pre or post-op radiotherapy HLFR Standard dose** = 41.4Gy in 23 fractions over 4.5 weeks (or equivalent) to PTVp_pre
- **Resectable pre or post-op radiotherapy HLFR Escalated dose** = 50.4Gy in 28 fractions over 5.5 weeks (or equivalent) total. Phase 1: 41.4Gy in 23 fractions over 4.5 weeks(or equivalent) to PTVp_pre, Phase 2: 9Gy in 5 fractions (or equivalent) to PTVp_post
- **Resectable pre or post-op radiotherapy SLFR Standard dose** = 41.4Gy in 23 fractions over 4.5 weeks (or equivalent) to PTVp_pre
- **Unresectable complete response (to induction chemotherapy) Standard dose** = 41.4Gy in 23 fractions over 4.5 weeks (or equivalent) to PTVp_pre
- **Unresectable incomplete response (to induction chemotherapy) HLFR Standard dose** = 50.4Gy in 28 fractions over 5.5 weeks (or equivalent) total. Phase 1: 41.4Gy in 23 fractions over 4.5 weeks (or equivalent) to PTVp_pre, Phase 2: 9Gy in 5 fractions (or equivalent) to PTVp_post
- **Unresectable incomplete response (to induction chemotherapy) HLFR Escalated dose** = 59.4Gy in 33 fractions over 6.5 weeks (or equivalent) total. Phase 1: 41.4Gy in 23 fractions over 4.5 weeks (or equivalent) to PTVp_pre, Phase 2: 18Gy in 10 fractions (or equivalent) to PTVp_post.
- **Unresectable incomplete response (to induction chemotherapy) SLFR Standard dose** = 50.4Gy in 28 fractions over 5.5 weeks (or equivalent) total. Phase 1: 41.4Gy in 23 fractions over 4.5 weeks (or equivalent) to PTVp_pre, Phase 2: 9Gy in 5 fractions (or equivalent) to PTVp_post

16.5.2 Dose Prescription and Dose Fractionation for involved lymph nodes

- 41.4Gy in 23 fractions over 4.5 weeks (or equivalent) to PTVn.
- For bulky residual involved lymph nodes only, Phase 2: 9Gy in 5 fractions (or equivalent) to PTVn_post

16.6 Radiotherapy treatment to metastatic sites

Patients with favourable metastatic disease, defined Modified Oberlin Prognostic Score of ≤1 (see section 16.2.2.5), will receive radical treatment of all metastases where feasible (standard of care).

Patients with unfavourable metastatic disease, defined as Modified Oberlin Prognostic Score of ≥2, will be randomised to receive radiotherapy to all sites of metastases where feasible versus loco-regional radiotherapy only.

16.6.1 Definition of Radiotherapy Target Volumes for Metastases

Radiotherapy should be delivered to the metastases at the same time as primary treatment but may be delivered sequentially where large volumes of the body require to be irradiated.
The GTV for metastases, will be defined as gross extent of metastasis at presentation on CT, PET and/or MRI. These will be named as per the International Naming Convention in the AAPM TG 263 report, and is detailed in the FaR-RMS QUARTET Radiotherapy Quality Assurance Guidelines. In case of discrepancy between imaging modalities, the larger volume should be delineated.

Margins for metastatic sites from GTV to CTV: 5 to 10 mm.

For exceptional cases with bulky macroscopic residual metastatic disease post induction chemotherapy margins from GTVmetastasis_post to CTVmetastasis_post should be 5 mm.

Expansion from the CTVs (or ITVs) to PTVs is to be undertaken as per local standard of care, based on the specific radiotherapy technique, image guidance strategy and set up errors, and is usually in the range of 3 to 10 mm.

16.6.2 Dose Prescription and Dose Fractionation for metastases

Radiotherapy dose and fractionation for specific sites is detailed in the FaR-RMS Radiotherapy and Imaging Manual, including fractionated radiotherapy for localized metastases, stereotactic ablative intracranial or body radiotherapy (for patients with limited metastatic disease only), whole lung, whole abdomen and whole brain. For the majority of metastases the intention will be to treat to an equivalent radiotherapy dose as detailed below.

- **Favourable metastatic disease** = Metastatic radiotherapy 41.4Gy in 23 fractions over 4.5 weeks (or equivalent)
- **Unfavourable metastatic disease** = Metastatic radiotherapy 41.4Gy in 23 fractions over 4.5 weeks(or equivalent)
- **Unfavourable metastatic disease** = No metastatic radiotherapy (radiotherapy only to primary tumour and involved regional lymph nodes).
- For bulky residual macroscopic metastatic disease only, where an initial Phase 1 of 41.4Gy in 23 fractions over 4.5 weeks (or equivalent) is to be delivered, Phase 2: 9Gy in 5 fractions (or equivalent) to PTVmetastasis_post.

16.6.3 Specific guidelines for metastatic radiotherapy:

-For bone, nodal and soft tissue metastases at other sites, 41.4Gy in 23 fractions or equivalent will be given.

-For one or more lung metastases, whole lung radiotherapy is given. The usual dose will be 15 Gy in 10 fractions.

-In cases of small volume and limited metastatic disease (≤ 3 metastases) stereotactic ablative body radiotherapy (SBRT) may be considered.

-In cases of malignant ascites, or diffuse peritoneal involvement, whole abdominal radiotherapy should be considered. The usual dose will be 24 Gy in sixteen fractions (or equivalent), followed by a boost to the primary tumour site (where identifiable) up to a dose of 41.4Gy (microscopic disease) or 50.4Gy (macroscopic disease).

-For patients with only limited brain metastases, where pre-treatment scans show a tumour volume ≤20cc, and no individual tumour with a diameter >3cm, these may be considered for stereotactic radiotherapy (SRT)

Whole brain radiotherapy may be considered for multiple brain metastases not suitable for SRT; the usual dose will be 30 Gy in 10 fractions.

-For lung only metastases with small volume and limited macroscopic residual metastatic disease, SBRT can be considered, in addition to whole lung RT and so doses should be adjusted to take this into account. Such exceptional cases should be discussed with the QUARTET RTQA experts.

Please see FaR-RMS QUARTET Radiotherapy Quality Assurance Guidelines for further details on the delineation, margins, radiotherapy techniques and Organ at Risk (OAR) dose constraints.

16.7 Radiotherapy Toxicity and Dose Modifications

All toxicity should be managed as per institutional practice/standard of care.

All dose delays and modifications should be managed as per institutional practice/standard of care however unscheduled interruptions to radiotherapy treatment should be avoided.

16.8 Radiotherapy supportive care

During radiotherapy patients should receive skin care, blood product support/ GCSF, antiemetics and analgesia when required as per local institutional guidelines.

16.9 Health Related Quality of Life - Questionnaires

All patients who participate in the radiotherapy randomisations RT1[A] and RT2 and the relapse randomisation CT3 will be provided with the appropriate health related quality of life (HRQoL) questionnaires (where the appropriate language version is available). See APPENDIX 12

17. RADIOTHERAPY QUALITY ASSURANCE PROGRAMME

Prospective radiotherapy quality assurance (RTQA) will be a requirement for all sites and patients included in the radiotherapy trial questions. This will be facilitated via the SIOPE QUARTET (Quality and Excellence in Radiotherapy and Imaging for Children and Adolescents with Cancer across Europe in Clinical Trials) initiative; this uses the existing EORTC Trials RTQA process, which is being used across Europe for a number of open EORTC studies in adult tumour types.

Pre-trial QA

All sites will be required to be approved for radiotherapy delivery via QUARTET. This will require evidence of a recent external output audit, end-to-end treatment plan verification via physical or virtual phantom, and completion of a facility questionnaire.

On trial – patient QA Radiotherapy plans for each individual patient should be uploaded to the EORTC system for approval, via their secure internet connection, prior to the commencement of radiotherapy treatment. This prospective review of target volumes and radiotherapy dosimetry, undertaken prior to the commencement of radiotherapy treatment, is mandatory for all patients treated in the radiotherapy randomisations, and is highly recommended for all patients. All planning information should be

submitted as soon as possible prior to start of treatment. Review and approval of each case should be performed within 48-72 hours. Please note that the feedback provided by the QUARTET initiative is advisory only and the responsibility for the treatment plan lies with the treating physician.

The following will be required as part of the individual case review (ICR):

- Treatment data of all patients must be submitted prior to the start of radiotherapy.
- All cases will be evaluated by the RTQA team before the start of treatment. Patients may not begin radiotherapy prior to plan approval by the RTQA team. Review should be performed within 48 to 72 hours.
- Feedback for the ICRs should be provided within 2 business days of submission. Plans requiring modification must be resubmitted within 2 business days. Reviews of resubmissions should be provided within 2 business days.
- Export all relevant diagnostic images in DICOM format and all patient treatment planning data in DICOM-RT format including:
- Cross sectional imaging (MRI, CT, PET-CT) from diagnosis and reassessment post induction chemotherapy (prior to local therapy)
- Operation note and histopathology results from surgery for all cases receiving postoperative radiotherapy
- Radiotherapy planning notes

See FaR-RMS QUARTET Radiotherapy Quality Assurance Guidelines for further information.

18. RADIOLOGICAL ASSESSMENTS

Radiological assessments should be conducted according to local practice. The suggested methods and time points are provided in Table 6: Schedule of Assessments for new diagnosed frontline patient – Frontline Assessments. There are no specific radiotherapy assessments. Monitor patients as per standard practice including induction chemotherapy assessments.

Tumour volume should each time be measured using the same technique and the same plane.

The current standards of care recommendation for radiological assessments for patients with RMS are produced and available via the EPSSG website. See APPENDIX 14

18.1 Definition of response

Local clinical/radiological response will be collected at each imaging time point. Where available as part of standard reporting, volumetric and RECIST response will also be collected

Further guidance can be found in the EpSSG Imaging Guidelines. See APPENDIX 14

Table 8: Overall tumour response

Primary Tumour	Metastatic Lesions	Regional Lymph Nodes	New Lesions	Overall Response
CR	CR	N	No	CR
CR	CR	PI	No	PR
CR	PR	N/PI	No	PR
CR	SD	N/PI	No	PR
PR	CR	N/PI	No	PR
PR	PR	N/PI	No	PR
PR	SD	N/PI	No	PR
SD	CR	N	No	PR
SD	SD	N/PI	No	SD
SD	PR	N/PI	No	SD
PD	Any	Any	Y/N	PD
Any	PD	Any	Y/N	PD
Any	Any	Any	Y	PD
Any	Any	PD	Y/N	PD

See APPENDIX 17 and APPENDIX 19 for further information.

19. CENTRAL RADIOLOGY REVIEW

A retrospective Quality Control review of all scans and cross sectional imaging (MRI, CT, Chest-CT), received as part of the radiotherapy QA review process for patients participating in the radiotherapy randomisations, prior to the commencement of local therapy, will be undertaken through the SIOPE EORTC QUARTET initiative.

In addition, a retrospective review of all FDG PET CT scans received at diagnosis and response assessment after 3 cycles as part of the FDG PET sub-study will be reviewed.

It is also strongly encouraged (not mandatory) to submit imaging for any scans conducted at the point of treatment failure/ relapse.

See FaR-RMS QUARTET Radiotherapy Quality Assurance Guidelines for further details.

20. FDG PET SUB-STUDY

This sub-study will be performed in SR, HR and VHR patients where FDG PET-CT or FDG PET-MRI scanning is available at diagnosis. Where facilities allow, and after routine staging with FDG PET -CT at diagnosis, patients in the sub-study will be offered a FDG PET-CT or FDG PET-MRI scan after 3 courses of induction chemotherapy to determine prospectively its prognostic value.

To achieve standardised uptake value harmonisation in a multi-centre setting, PET-CT scans should be performed as per the current EANM recommendations [84].

Response will be scored as complete remission, partial remission, stable disease or progressive disease according to PERCIST 1.0 criteria [81] and visual 'Deauville like' criteria. The prognostic value of response will be related to EFS and local failure free survival.

Central review of the FDG-PET scans by consensus reading will be supported by the SIOP Europe QUARTET radiology review platform.

Where a FDG PET-CT is not routine practice after 3 courses, the patient may consent to participate in the sub-study if a baseline FDG PET-CT scan is available. Consent must be obtained prior to undertaking any non-standard scans. Participation is optional for the site and patient.

See FDG-PET FaR-RMS study and imaging upload manual for further information.

21. DIFFUSION WEIGHTED MRI SUB-STUDY (FRONTLINE)

This sub-study will be coordinated by the Princess Máxima Center and will investigate the prognostic value of changes in diffusion MRI parameters of the primary tumour as response to induction chemotherapy. The aim is to assess whether changes in diffusion, measured by the apparent diffusion coefficient (ADC), reflect tumour response to chemotherapy, and thereby could be used as a prognostic imaging biomarker.

The study may be performed in all, localised and metastatic, frontline RMS patients, where DW-MRI is available at diagnosis and after 3 courses of induction chemotherapy. MRI is the primary modality for imaging of the primary tumour; the EpSSG imaging guideline recommends the use of DW-MRI as standard of care.

MRI scans made of the primary tumour at baseline and after 3 cycles of chemotherapy will be primarily collected in QUARTET either as part of the RTQA procedure or via separate upload via the QUARTET imaging platform (Keosys).

The FaR-RMS patient information sheet consent will be asked for central collection and analysis of imaging.

See DW-MRI FaR-RMS study and imaging upload manual for further information.

Also see APPENDIX 15.

22. PATIENT FOLLOW-UP

Following completion of treatment, the frequency of follow-up assessments should be as per local practice, with reference to the EpSSG guidelines.

It is suggested that the frequency of follow-up assessments should be every 3-4 months for the first 3 years.

Disease related follow-up checks should include

- Physical examination at each visit
  - Appropriate imaging of primary tumour; for superficial tumours ultrasound may be used. In all other cases MRI is the preferred imaging modality.
-
- -Chest radiograph (if an abnormality is found a CT of the chest) Cardiac assessments (if applicable)

A progression/relapse form should also be completed (where applicable).

Follow-up information must be provided for a minimum of 3 years following study entry. Patients will be followed up for progression and death until the end of trial definition has been met.

For CT3: Patients will be followed up for a minimum of 6 years from trial entry (or 5 years from end of relapsed trial treatment, whichever comes later). Patients will be followed up for progression and death until the end of trial definition has been met.

Post therapy all patients should be followed up for possible tumour relapse and treatment side effects, as described in Table 6: Schedule of Assessments for new diagnosed frontline patient and Table 7: Schedule of Assessments for relapsed patients.

23. TREATMENT DISCONTINUATION AND PATIENT WITHDRAWAL

23.1 Treatment Discontinuation

If a patient stops FaR-RMS protocol treatment, the reason should be recorded in the patient's medical records and be reported on the appropriate CRF whether it is due to either the patient's, parent/legal guardian's or clinician's decision. Reasons for stopping protocol treatment may include, but are not limited to:

- The patient and/or patient's parent/guardian does not wish to continue with further trial treatment
- Unacceptable toxicity
- Disease progression whilst on therapy
- Pregnancy (where the patient's decision is to proceed with the pregnancy)

FAR-RMS will be analysed on an intention-to-treat (ITT) basis and all patients who stop randomised trial treatment will remain in the trial for follow-up unless the patient and/or parent/legal guardian explicitly withdraws consent for data collection.

Withdrawal of consent to data collection: the patient and/or parent/legal guardian may withdraw consent at any time during the study. For the purposes of this trial, withdrawal is defined as:

- The patient is not willing to be followed up for the purposes of the trial at any further visits (i.e. only data collected prior to the withdrawal of consent can be used in the trial analysis)

The details of withdrawal should be clearly documented in the patient's medical records. A Withdrawal of Consent Form should be completed.

A patient's wishes with respect to his or her data must be respected.

23.2 Loss to follow-up

If a patient is lost to follow-up, every effort should be made to contact the patient's primary physician (GP in the UK) to obtain information on the patient's status. Similarly, if a patient's care is transferred to another clinician, the applicable National Coordinating Centre (NCC) should be informed and follow-up information be obtained.

24. BIOLOGICAL AND PATHOLOGICAL STUDIES

For all cases, a formalin fixed paraffin embedded (FFPE) block together with the Pathology report, if available, and molecular results, if available, should be sent to the National Pathology Coordinator as soon as possible after diagnosis.

24.1 Samples for Pathological analyses

Formalin fixed paraffin embedded (FFPE) blocks and slides are an essential part of the FaR-RMS trial for pathology review and assessment of fusion gene status (see APPENDIX 13). They will also support future biological studies. Where tissue is available from routine procedures, the following samples should be made available for use in the FaR-RMS study:

	At Diagnosis	At Second Surgery	At Relapse
Representative paraffin embedded tumour block: - Send at room temperature to pathology national review centre	●	●	●
A full set of H&E slides from each FFPE block: Send at room temperature to pathology national review centre	●	●	●

In addition, it is also strongly encouraged that samples (e.g. frozen tumour, blood, plasma, bone marrow, etc) are collected in accordance with national biobanking and molecular profiling initiatives for future biological studies.

In the UK (and where approved in other countries, and where the patient provides consent, the following samples will be collected and stored within the Children's Cancer and Leukaemia Group (CCLG) Tissue Bank at the University of Newcastle (UK REC approval 18/EM/0134).for future biological studies.

	At Diagnosis/prior to first cycle	Post induction cycles 1,2,3,6,9,	During maintenance (every 6 months every 3 months (VHR) HR)	At Relapse
Bone Marrow (BM) (EDTA) up to 5ml	●			●
Bone Marrow (PAXgene®) up to 5ml	●			●
~5ml whole blood (EDTA) For constitutional DNA	●			●
~5ml whole blood (PAXgene®)	●			●
Up to 10m whole Blood (EDTA) for circulating DNA		●	●	●
Snap Frozen tumour:(-80ºC or liquid nitrogen)	● **And second surgery**			●

More information is provided in the EpSSG Pathology Guidelines, the FaR-RMS National Pathology Manual and FaR-RMS National Biology Manual.

For patients participating in the relapse question, CT3, see Table 7: Schedule of Assessments for relapsed patients.

25. ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with EU Directive for Clinical Trials 2001/20/EC and the Detailed Guidance on the Collection, Verification and Presentation of Adverse Events/Reaction Reports Arising From Clinical Trials of Medicinal Products For Human Use ('CT-3'). Definitions of different types of AE are listed in APPENDIX 8.

All AEs and ARs as defined in APPENDIX 8 will be collected and recorded in the patients' medical records. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the patient's medical records - source data) with reference to the Summary of Product Characteristics.

During CT3 (relapse) causality of all AEs will also be recorded on the CRF.

25.1 Reporting Requirements

25.1.1 Adverse Events and Adverse Reactions

For definitions of Adverse Event (AEs) and Adverse Reactions (ARs) refer to 0

As the safety profiles of the IMPs used in this trial are well characterised, only selected ARs experienced during treatment will be reported. The highest grade of AR experienced during each cycle of chemotherapy will be recorded only.

The exception is during the Phase 1b component when all Grade 3 and 4 AEs will be recorded and during CT3 (relapse) all grades of all AEs that meet the definition of CTCAE will be reported and recorded. Clinically significant abnormalities (including laboratory abnormalities, examinations (e.g., ECGs, vital signs, chest x-rays) should also be reported.

Adverse events only need to be reported for those participating in a trial treatment question. Patients who register on the study but subsequently enter no trial registrations or randomisations do not need to report adverse events.

25.1.2 Serious Adverse Events

Investigators should report AEs that meet the definition of a Serious Adverse Event (SAE) (see 0 for definition) and that are not excluded from the reporting process as described below.

25.1.3 Events that do not require reporting on a Serious Adverse Event Form

The following events should not be reported on an SAE Form:

- Hospitalisations for:
  - Protocol defined treatment
  - Pre-planned elective procedures unless the condition worsens
  - Treatment for the symptoms of /progression of the patient's cancer
  - Progression or death as a result of the patient's cancer, as this information is captured elsewhere on the CRFs

Hospitalisations for the following events should be reported on an **Expected SAR Form** rather than an SAE Form (unless the condition is life threatening or proves fatal):

Please note these exceptions do not apply to patients entered into the relapse (CT3) trial question.

- Fever
- Infections
- Haematological toxicity:
  - Anemia
  - Lymphocyte count decreased
  - Neutrophil count decreased
  - Platelet count decreased
  - White blood cell decreased
- Gut toxicity:
  - Diarrhoea
  - Nausea
  - Vomiting
  - Mucositis

- Constipation

Expected SAR Forms should be completed by sites as soon as possible once the event has resolved and sent via post, email or fax to the UK Coordinating Centre for data entry.

The Sponsor will monitor expected SARs for any increase in specificity, frequency or severity of expected SARs.

25.1.4 Monitoring pregnancies for potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

In the event that a patient or their partner becomes pregnant during the SAE reporting period, complete a Pregnancy Notification Form (providing the patient's details). If it is the patient who is pregnant, outcome data should be provided on a follow-up Pregnancy Notification Form. Where the patient's partner is pregnant, consent must first be obtained and the patient should be given a *Release of Medical Information Form* to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy, they should sign the *Release of Medical Information Form*. Once consent has been obtained, details of the outcome of the pregnancy should be provided on a follow-up Pregnancy Notification Form. If appropriate, an SAE Form should also be completed as detailed below.

25.1.5 Reporting period

Details of all ARs and SAEs (except those listed above) will be documented and reported from the date of registration/randomisation in to a treatment question until 30 days after the administration of the last treatment.

Except for:

Acute post-local therapy complications will be collected until 120 days after the start of first local therapy.

Long term radiotherapy and surgical toxicity will be recorded and reported until the end of patient follow-up.

25.1.6 Post study SARs and SUSARs:

SAEs that are judged to be at least possibly related to the IMP(s) must still be reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

25.2 Reporting Procedure

25.2.1 Site

Adverse Reactions

ARs experienced during treatment should be recorded on the CRF. ARs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4 (see APPENDIX 9). Any ARs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AR Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded. The exception is during the Phase 1b component when all Grade 3 and 4 ARs will be recorded and during CT3 (relapse) all grades of all AEs that meet the definition of CTCAE will be reported and recorded. Clinically significant abnormalities (including laboratory abnormalities, examinations (e.g., ECGs, vital signs, chest x-rays) should also be reported.

Surgical complications will also be reported using the Clavien-Dindo scale (see APPENDIX 10).

Serious Adverse Events

For more detailed instructions on SAE reporting, refer to the SAE Form Completion Guidelines contained in the Investigator Site File (ISF).

AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 25.1.3 above) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be sent to the UK Coordinating Centre, based at the CRCTU, as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE

Email: reg@trials.bham.ac.uk

Include "FaR-RMS SAE" in the subject line

Or fax the SAE Form with an SAE Fax Cover Sheet to (only if email is not possible):

+44 (0) 121 414 9520 or +44 (0) 121 414 7989

On receipt, the UK Coordinating Centre will allocate each SAE a unique reference number. This number will be transcribed onto the SAE which will then be sent back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day, please contact the UK Coordinating Centre. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE completed by the UK Coordinating Centre should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the UK Coordinating Centre in the post and a copy kept in the ISF.

Investigators should also report SAEs within their own institution in accordance with local practice.

Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

25.2.2 UK Coordinating Centre

On receipt of an SAE Form, seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. not defined in the Reference Safety Information or protocol), it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR) or an unexpected and related SAE.

The Sponsor will monitor SAEs for any increase in specificity, frequency or severity of expected SARs

If any of the following complications arise and are related to radiotherapy, they will be regarded as 'expected events' for this trial:

25.2.3 Common Toxicities Radiotherapy

Site	Acute	Late
General	Dermatitis radiation Anaemia Thrombocytopenia Neutropenia Mucositis Nausea Vomiting Fatigue Pain Wound complication Wound infection Weight Loss Anorexia Hair loss Fever	Reduced growth of irradiated bones/ tissues Vascular disease Fibrosis Fracture risk Tissue/ Brain necrosis Peripheral Nerve injury Avascular necrosis Second malignancy Kyphosis/ Scoliosis Muscular weakness Myelitis Anxiety/ Depression Haemorrhage Hair loss Skin hypo/ hyper- pigmentation/ atrophy
Head & Neck	Hoarseness Lethargy/ Somnolence Difficulty swallowing	Dry Eye Optic nerve disorder Retinopathy Watering Eyes Cataract Hypopituitarism Hypothyroidism Hearing Impairment Cognitive disturbance Memory impairment Stroke Tinnitus Trismus Dry mouth Dental Caries
Thorax	Dyspnea Cough Esophagitis	Cardiac disorders Dyspnea Cough
Abdomen/ Pelvis	Abdominal Pain Diarrhoea Constipation Urinary frequency/ urgency Haematuria	Lower GI haemorrhage Spleen disorder Diarrhoea Constipation Colitis Fecal incontinence/ urgency Hepatobiliary disorders Chronic kidney disease

		Sexual dysfunction Infertility Haematuria Urinary frequency/ urgency Urinary incontinence
Limbs		Joint range of movement decreased Lymphoedema

25.2.4 Reporting to the Competent Authority and Research Ethics Committee

Suspected Unexpected Serious Adverse Reactions

Individual events categorised as SUSARs will be reported to the EudraVigilance Clinical Trial Module (EVCTM) and to each non-EU country as required.. Events will be reported in accordance within the regulatory specified time frame:

- Fatal or life threatening SUSARs within a maximum of 7 days with a detailed follow-up report within an additional 8 days
- All other SUSARs within a maximum of 15 days

The UK Coordinating Centre will provide SUSARs reports to the NCCs who will report SUSARs to the relevant REC and Competent Authority (where required) , within the time frame specified above, and Principal Investigators within their country. The UK Coordinating Centre will assume responsibility for reporting to these parties in the UK.

Unexpected and related SAEs

The UK Coordinating Centre will report all events categorised as Unexpected and Related (to radiotherapy) SAEs to the main Research Ethics Committee (REC) within 15 days.

Development Safety Update Report

The UK Coordinating Centre will include details of all SAEs, SARs (including SUSARs) in a Development Safety Update Report (DSUR) produced annually from the date of the first Clinical Trial Authorisation received for the trial to the submission of the End of Trial Declaration. NCCs will be provided with a copy of this report and where contractually required to do so will forward this report to the relevant Competent Authority and REC.

Adverse Reactions

Details of all ARs will be reported to Competent Authorities on request.

Other safety issues identified during the course of the trial

The NCCs will notify the relevant Competent Authority and REC immediately if a significant safety issue is identified during the course of the trial. The UK Coordinating Centre will notify the MHRA and UK REC.

Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

Manufacturer of Investigational Medicinal Product

All SAEs in CT3 will be reported to Bayer within 24 hours of receipt.

26. DATA HANDLING, RECORD KEEPING AND DATA COLLECTION

The FaR-RMS trial will use an eRDE system which will be used for completion of the Case Report Form (CRF). Access to the eRDE system will be granted to individuals via the UK Coordinating Centre. Users will be provided with training which will be documented.

SAE reporting will be paper-based.

If the eRDE system is unavailable for an extended period of time a paper based CRF should be completed and forms returned to the applicable NCC for data entry.

The CRF must be completed by an Investigator or an authorised member of the site research team (as delegated on the site signature and delegation log, or country specific equivalent) within the timeframe listed in the eRDE.

Entries on the paper CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be indicated on the form. Missing and ambiguous data will be queried. All sections are to be completed before being submitted.

In all cases, it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

The CRF may be amended by the UK Coordinating Centre, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt, and acknowledgement of receipt and implementation should be sent to the applicable NCC if required.

27. ARCHIVING

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed ICFs, ISF, Pharmacy Files, patients' medical records, copies of SAE forms, etc.) at their site are securely retained for at least 25 years after the end of the trial. NCCs will notify sites when documentation can be destroyed.

28. QUALITY MANAGEMENT

28.1 Site Set-up and Initiation

Sites will be set up and initiated by the applicable NCC. All sites will be required to sign a clinical study site agreement (or country specific equivalent) prior to participation. In addition, all participating Investigators will be asked to supply a current CV. All members of the site research team will also be required to sign the site signature and delegation log (or country specific equivalent).

Prior to commencing recruitment, all sites will undergo a process of initiation. It is anticipated that key members of the site research team will be required to attend either a meeting or a teleconference

covering aspects of the trial design, protocol procedures, AE reporting, collection and reporting of data and record keeping.

It is anticipated that sites will be provided with an ISF and a Pharmacy File containing the documentation and instructions required for the conduct of the trial by the NCC. The applicable NCC must be informed immediately of any change in the site research team.

28.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the UK Quality Management Plan and the International Monitoring Plan.

Investigators will allow the FaR-RMS trial staff (or 3rd party contract research organisation) access to source documents as requested.

28.3 Central Monitoring

If allowed by country specific legislation/guidance and if the patient and/or parent/legal guardian has given explicit consent, sites are requested to send in copies of signed ICFs to the applicable NCC for in-house review.

Trial research staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trial research staff will check incoming data for compliance with the protocol, data consistency, missing data and timing. Sites will be sent requests for missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or Good Clinical Practice (GCP), and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group (TMG), Trial Steering Committee (TSC) and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol.

28.4 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review and regulatory inspections at their site, providing direct access to source data/documents.

Sites are also requested to notify the applicable NCC of any inspections by the relevant Competent Authority.

NCCs will notify the UK Coordinating Centre of any significant audit findings.

28.5 Notification of Serious Breaches

Country specific legislation may require the NCC to notify the Competent Authority and Ethics Committee in writing within 7 days of becoming aware of any serious breach of:

- The conditions and principles of GCP in connection with the trial
- The protocol relating to the trial

A “serious breach” is a breach which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the patients in the trial
- The scientific value of the trial

Sites are therefore requested to notify the applicable NCC of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the applicable NCC is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the applicable NCC in providing

sufficient information to report the breach to the relevant regulatory authorities where required and in undertaking any corrective and/or preventive action.

Please note: persistent failure by sites to provide prompt and accurate information, particularly with regard to the reporting of SAEs, can be considered a serious breach.

The NCC will notify the UK Coordinating Centre of any serious breaches.

29. END OF TRIAL DEFINITION

The trial will remain open until the date of the last patient's last visit; end of follow-up. The applicable NCC will notify the relevant Competent Authority and Ethics Committee that the trial has ended at the appropriate time and will provide them with a summary of the clinical trial report within 6 months of the end of trial.

30. STATISTICAL CONSIDERATIONS

30.1 Randomisation procedure

For each randomisation, the randomisation program will allocate treatment via a computerised minimisation algorithm. Patients will be allocated in a 1:1 ratio for each randomisation. All of the required information on stratification factors must be available at the time of randomisation. Patients will be stratified by the following factors for each randomisation:

Table 9: Minimisation factors for each randomised question

Randomisation		Minimisation factors
Radiotherapy	1a	Risk Group Assignment subgroup (SR, HR and VHR) Age (yrs) at diagnosis (≤10, >10 and ≤18, >18) Allocation to VHR or HR randomisation (treatment options as per VHR or HR randomisation / not randomised for induction). Size of tumour in cm at initial diagnosis (≤5 / >5*) Site of tumour at initial diagnosis (favourable / unfavourable) Type of disease at diagnosis (local vs metastatic)
	1b	Risk Group Assignment subgroup (B/C/D/E/F/G/H) Age (yrs) at diagnosis (≤10, >10 and ≤18, >18) Allocation to VHR or HR randomisation (treatment options as per VHR or HR randomisation / not randomised for induction) Allocation to randomisation 1a (pre-op / post-op / not randomised to 1a elected pre-op / not randomised to 1a elected post-op) Size of tumour in cm at initial diagnosis (≤5 / > 5*)
	1c	Risk Group Assignment subgroup (B/C/D/E/F/G/H) Age (yrs) at diagnosis (≤10, >10 and ≤18, >18) Allocation to VHR or HR randomisation (treatment options as per VHR or HR randomisation / not randomised for induction) Size of tumour in cm at initial diagnosis (≤5 / > 5*)
	2	Age (yrs) at diagnosis (≤10, >10 and ≤18, >18)

		Allocation to VHR randomisation (treatment options as per VHR randomisation / not randomised for induction) Bone and/or bone marrow involvement at initial diagnosis (no / yes)
Newly diagnosed chemotherapy	Very high risk induction	Risk Group Assignment subgroup (G/H) Age (yrs) at diagnosis (≤10, >10 and ≤18, >18) Number of metastases ≤2 or >2
	High risk induction	Risk Group Assignment subgroup (D/E/F) Age (yrs) at diagnosis (≤10, >10 and ≤18, >18)
	Very high risk maintenance	Same stratification factors as per VHR induction randomisation. Allocation to VHR randomisation (treatment options as per VHR randomisation /not randomised for induction)
	High risk maintenance	Same stratification factors as per HR induction randomisation. Allocation to HR randomisation (treatment options as per High risk randomisation / not randomised for induction)
Relapse		Radiotherapy prior to relapse randomisation (no radiotherapy / any radiotherapy). Relapse type (metastatic / loco-regional): locoregional is primary site and/or regional draining lymph nodes; metastatic is distant lymph nodes and other sites PAX-FOXO1 fusion status (from first diagnosis or relapse) (negative / positive / unknown). Age (yrs) at diagnosis (≤10, >10 and ≤18, >18) Prior irinotecan (no/yes) Prior relapse treatment (no/yes) * * *No' is the equivalent to where the patient has received only frontline therapy (one prior line of therapy); 'Yes' is the equivalent to where the patient has also previously received at least one line of relapse treatment (more than one prior line of therapy).*

*Includes patients that are assessed as not evaluable, they will be included in >5cm group.

30.2 Trial Design – General Principles

In rare diseases, it may not be possible to obtain the same level of evidence on treatment efficacy as with commoner diseases. We take the view that any randomised evidence is better than none, and certainly better than the alternative of non-randomised comparisons with their likely biased estimates of treatment effect [85]. For example, in the recent RMS 2005 trial , the control group in one of the randomised comparisons did 15% better than anticipated in the sample size calculation; the experimental arm was no better than the control but, had the trial used a historical comparison, it would have appeared much better. Hence, randomised comparisons – if properly conducted – provide unbiased estimates of treatment effect, but the confidence intervals may be wide in rare diseases, requiring more cautious interpretation.

It may, therefore, be appropriate to use relaxed criteria for decision making. In some circumstances, a lower level of certainly that the standard 97.5% (i.e. 2p=0.05, equivalent to 1p=0.025) may be acceptable. For example, when comparing one drug with another (or one regimen with another), a 75% probability that one is better than the other may be adequate, especially if there are no major differences in toxicity. If new drugs are being added or treatment is being intensified, a higher level of certainly may be required but, if it is the best that can be achieved within the confines of small patient population, a 95% or even 90% chance that the new treatment is better may be acceptable, rather than the standard 97.5% chance. If there is a 90% chance that one treatment is better, the correct one will be selected 9 out of 10 times (under a hypothesis-testing approach, effective treatments that have not quite reached the level of significance required would be concluded, inappropriately, to be ineffective – i.e. the null hypothesis that there is no difference would not be rejected). Via simulations, it has been demonstrated that, over the longer time frame (20-30 years), accepting such a more relaxed level of evidence will lead to improved outcomes for patients and should be viewed as a long-term strategy [86].

Hence, a Bayesian framework is preferred to a frequentist one; though, because of greater familiarity with frequentist ideas, either a frequentist approach only has been used where patients numbers permit a plausible conventional (e.g. 2p=0.05, power=80%) sample size calculation or a frequentist calculation along with a Bayesian design has been provided. Under a Bayesian approach, using non-informative priors, the posterior probability distribution is plotted and the probability that one treatment is better [i.e. P(true HR<1.0|data)=X] – or better by a specified amount (e.g. P(true HR<0.8|data)=Y) – is given. This seems conceptually easier for clinicians and patients to understand than either a p-value (often interpreted wrongly) or an estimate of effect size with a measure of the uncertainty surrounding it. Bayesian analysis also avoids potential issues of whether to used one-sided or two-sided p-values.

A further benefit of a Bayesian approach is that interpretation is based on the observed results, so prior assumptions are less important, both with regard to estimated effect sizes – often little more than guesswork in rare diseases – and design considerations (e.g. whether a superiority or a non-inferiority trial).

Also, in a Bayesian framework, the distinction between primary and secondary outcome measures may be less important. Decisions as to which treatment is the better/best may be made using a holistic approach, taking account of all relevant outcome measures (albeit with a hierarchy of importance, rather than dichotomisation into primary and the rest).

One possible conclusion from a Bayesian approach is that there remains uncertainty and, assuming still of clinical interest, the randomisation should continue (either in the next trial or, as below, in a continuation of FaR-RMS). Hence, it may be sufficiently clear that a novel agent does work (e.g. 95% chance that true HR<1.0) or does not work (e.g. 95% chance that true HR>0.9, with HR>0.9 not being a sufficiently large clinical benefit), while there may be uncertainty (e.g. 90% chance that true HR<1.0, where 90% is not considered strong enough evidence) and more data should be gathered (note that in the latter scenario, under a hypothesis-testing approach, the frequentist p-value is 2p=0.2 and a possibly effective treatment would have been rejected based on an artificial dichotomisation at 2p=0.05).

The risks of accepting an inferior treatment will depend on how inferior it is. If there is a true large difference, it will probably be detected and the correct treatment selected; if any true differences are small, it will not matter too much if a slightly suboptimal treatment is selected. In some cases, the conclusion might be that more than one treatment is acceptable and patients can be offered a choice.

Multi-arm multi-stage (MAMS) designs are a very efficient way to evaluate several novel agents/regimens, without needing to set up a new trial each time. This is particularly the case in the current regulatory framework for international trials, where the amount of work and time needed to open several countries can be substantial. Hence, FaR-RMS is intended to provide a framework for the

introduction of new arms – and the early dropping of ineffective ones – in a rolling programme that will extend beyond the initial grant award period.

FaR-RMS has several randomisations and, given the difficulties of performing realistic sample size calculations with small patient numbers, each of these will be treated as independent and there will be no family-wise adjustment of error rates where a frequentist approach is being used (in any case, it can be argued that this is not necessary). There are no clear clinical reasons to expect interactions (e.g. between radiotherapy doses or timing and the drugs given in induction), but the presence of interactions will be explored at the analysis stage.

30.3 Outcome Measures

The trial outcome measures are defined in Section 2.

30.4 Sample Size Considerations

The sample size is pragmatic and based on the number of patients that can be recruited in Europe over the trial's accrual period. Non-compliance and loss to follow-up are expected to be very low, so the sample size does not take this into account. The approximate number of patients anticipated for each group is presented in Table 2: Recruitment per group. For the randomised questions analysed using Bayesian methods, specific decision guidelines were chosen based on the primary outcome in order to assist treatment selection decisions at the main analysis. In general, a therapy may be chosen, based on the posterior probability at the main analysis if Pr (true effect is < h*, given observed data) > p*, where h* is the upper limit and p* is the cut-off of the lower level of certainty (i.e. there is a probability p* that the true effect in one of the therapy arms is greater than some clinically relevant value h*). The design parameters h* and p* were chosen on the basis of the operating characteristics of the study design (and their clinical interpretation) and were examined in simulation studies. Where a Bayesian probability-based approach is adopted for survival outcomes, a Normal-Normal conjugate analysis for log Hazard Ratio is used, including assessing the design characteristics. The normal approximation for the log Hazard Ratio with variance 4/n is assumed, where n=total number of events in both arms [87]. Operating characteristics were calculated by simulating data for 10,000 trials under different possible underlying true effect sizes and decision guidelines. For the randomised questions using a frequentist approach, sample size was derived using *stpower logrank* and *nstage* commands in Stata v14. The results of the simulations and further details on the calculations are given in the Statistical Analysis Plan. The guidelines for randomised questions are detailed in Table 10: Decision guidelines for each randomised question .

Table 10: Decision guidelines for each randomised question

Randomisation		Trial design	Baseline 3-year primary outcome *	Decision guideline at the interim analysis	Decision guideline at the final analysis
Radiotherapy	1a	Bayesian	80%	A minimum of 35 patients being entered during year 3 of the trial.	Experimental treatment may be accepted if Pr(trueHR<1|data)≥70 % and control if Pr(trueHR>1|data)≥70 %.
	1b	Phase II	79%	No formal interim analysis is planned.	Triggered by 52 events in total; the experimental treatment may be accepted if two sided p value < 0.20.
	1c	Phase II	72%	No formal interim analysis is planned.	Triggered by 76 events in total; the experimental treatment may be accepted if two sided p value < 0.20.
	2	Phase II, Bayesian	35% to 40%	No formal interim analysis is planned.	The control treatment may be accepted if Pr(trueHR<1|data)≥70 % and the experimental treatment may be accepted if Pr(trueHR>1|data)≥70 %.
Newly diagnosed chemotherapy	Very high risk	Bayesian selection	35%	Triggered by at least 50 patients per arm, stop recruitment to experimental arm if observed if Pr(trueHR>1|data)>70 %.	Further 50 patients per arm; the treatment may be selected if Pr(trueHR<1|data)>80%.
	High risk	MAMS, superiority	65%	Stage 1: triggered by 37 events in the control arm; stop recruitment to experimental arm if observed HR>0.887.	Triggered by 102 events in the control arm; the experimental treatment may be accepted if one-sided p value <0.05.
	Very high risk mainten-ance	Phase III, superiority	35% to 45%	No formal interim analysis is planned.	The experimental treatment may be accepted if one sided p value < 0.20.

	High risk mainten-ance	Phase III, superiority	65%	No formal interim analysis is planned.	The experimental treatment may be accepted if one sided p value < 0.20.
Relapse		MAMS, superiority	30% at 1 year	Stage 1: triggered by 23 events in the control arm; stop recruitment to experimental arm if observed HR>1.00. Stage 2: triggered by 42 events in the control arm; stop recruitment to experimental arm if observed HR>0.892.	: Triggered by 105 events in the control arm; the experimental treatment may be accepted if one sided p value < 0.05.
		It is anticipated that baseline 1-year EFS will be 30% in the control treatment arm, based on previous studies. A hazard ratio (HR) of 0.66 would equate to a 15% absolute improvement in 1-year EFS to 45%. This difference is considered clinically worthwhile. The proposed Phase II trial is designed as part of a seamless Phase II/III trial. The Phase II part has a 1-sided alpha of 0.2 and power of at least 80%. A minimum of 130 patients will be randomised in a 1:1 ratio between the experimental and control arms. Phase II (stage 2) analysis will be performed when at least 42 events have occurred in the control arm. If the observed one-sided p-value is >0.2, it will be concluded that the experimental arm is not effective; if the one-side p-value is <0.01, the experimental arm will be accepted as being definitely effective; if the one-sided p-value is between these values, the trial should proceed to Phase III. In Phase III, 260 patients (130 per arm) and about 105 events in the control arm are required to give 80% power at a 1-sided alpha of 0.05. Accrual both the Phase II (stage 2) and Phase III components will be managed – i.e. accrual of patients aged 18 or over may be suspended – in order to ensure that at least 70% of patients are less than 18 years old. An interim futility analysis (stage 1) is planned when approximately 23 events have been observed in the control arm. if observed HR>1.00, recruitment will be stopped and futility concluded. The probability of observing a HR>1.0 if the true HR=0.66 is 0.09.			
The primary outcome for each question is detailed in Table 1: Outcome Measures.					

30.5 Analysis of Outcome Measures

The analysis of the outcome measures will be according to the intention-to-treat principle. Trial recruitment will not be interrupted while performing interim analyses. For the randomised questions analysed using Bayesian methods, the main analysis based on the primary outcome measure will result in a posterior probability distribution. The analysis will use non-informative priors. For the randomised questions using a hypothesis-testing approach, the main analysis based on the primary outcome measure will result in a point estimate, confidence intervals and associated p-values derived from a

model adjusted for stratification factors. For all randomisations, a decision on which therapy will be taken as the standard will be made at this stage, taking into account secondary outcome measures. Non-randomised groups will be summarised using descriptive statistics as these have no comparative questions; there will be no comparison with historical data and the aim of data collection for these groups is for biological studies. Further details of the planned statistical analysis are provided in a separate Statistical Analysis Plan.

30.6 Planned Subgroup Analyses

Exploratory subgroup analyses will be performed for known prognostic factors, including stratification parameters. Given the well-known dangers of subgroup analyses, all analyses will be treated as hypothesis-generating.

30.7 Planned Interim Analysis

For all randomised groups, data will be analysed and reported at least annually to an independent DMC. The DMC may also recommend stopping or modifying the trial (or part of the trial) if any issues are identified which might compromise patient safety, for clear evidence of efficacy or because of poor accrual or data quality. Further, table 10 provides when interim analysis for each of the questions within the study are planned, if any.

30.8 Planned Final Analyses

The first main analyses will be performed three years after randomisation of the last patient or longer for maintenance randomisations. This does not preclude preliminary analyses being performed earlier.

30.9 Stopping Guidelines

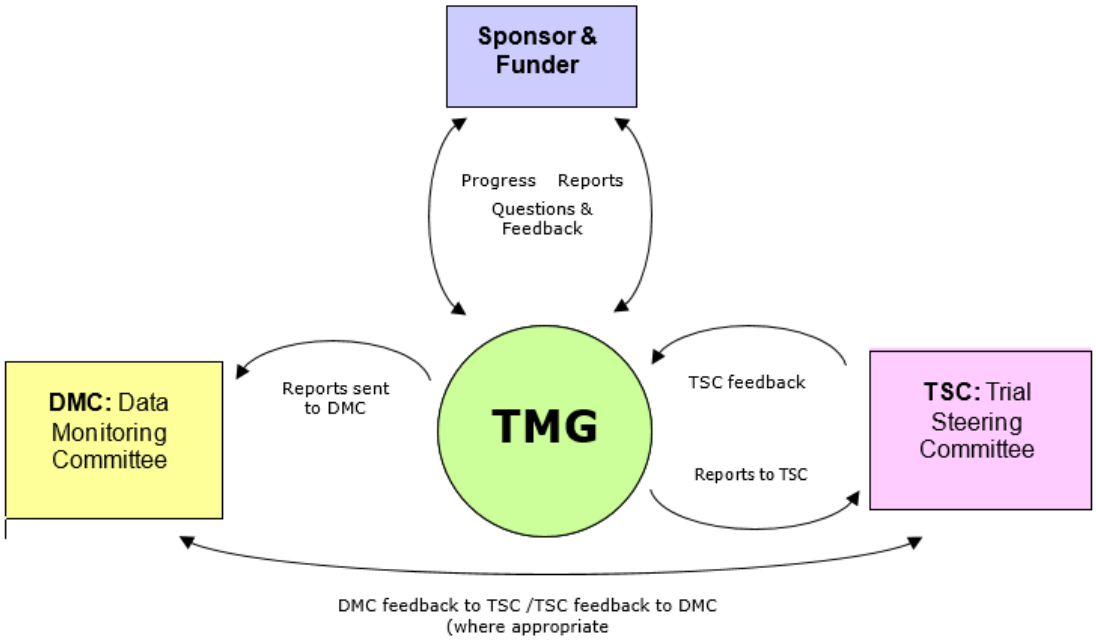
The independent DMC will review the safety data and efficacy at regular intervals and will make recommendations to the TSC if they have concerns regarding any of the randomised groups.

30.10 Handling Missing data

The Primary outcome for each question in the study is a time to event outcome, and in survival analysis, patients that have withdrawn, lost to follow up or have missing data will be censored at the time we last have data on the patient if they have not had the event of interest. On the other hand, for Phase 1b we will recruit very few patients and we do not expect any missing data. However, if patients withdraw before DLT period is completed for reasons other than toxicity and are deemed as missing outcome (not evaluable) they will be replaced.

31. TRIAL ORGANISATIONAL STRUCTURE

Figure 13: Trial Organisational Structure



31.1 Coordinating Sponsor

The University of Birmingham is the Coordinating Sponsor. In addition, the University of Birmingham (UK Coordinating Centre) will undertake the responsibilities of NCC in the UK.

NCCs are responsible for the conduct of the trial within their own country.

31.2 National Coordinating Centres (NCCs)

The Coordinating Sponsor has delegated the set-up, management and analysis of the trial to the UK Coordinating Centre. The role of the UK Coordinating Centre is assumed by the CRCTU, University of Birmingham. The trial will be set-up, managed and analysed in the UK in accordance with CRCTU standard policy and procedures.

Each NCC (see the introductory pages for the list) will manage the trial in its country in accordance with the trial protocol and their standard policy and procedures.

31.3 Trial Management Group

The TMG is composed of the Chief Investigator, co-investigators, representatives from each NCC, biology, pathology and radiology leads and the trial team at the CRCTU. The TMG is responsible for the day-to-day running and management of the trial and will meet by teleconference or in person at least every 3 months.

31.4 Trial Steering Committee

The TSC will provide oversight of the trial and provide advice through its independent chair. The TSC will include a patient representative and a Sponsor's representative. The Chief Investigator will report to the TSC on behalf of the TMG. The TSC will assume responsibility for the oversight of the trial on behalf of the Coordinating Sponsor. The TSC will meet or hold teleconferences at least once a year during the treatment period, or more often if required.

31.5 Data Monitoring Committee

Analyses will be supplied in confidence by the trial statistician to an independent DMC. In the light of these analyses, and the results of any other relevant trials, the DMC will advise the TSC if, in their view, the randomised comparisons in the FaR-RMS trial have provided **both** (i) "proof beyond reasonable doubt" that for all, or some specific types, of patient, any of the randomised treatments are clearly indicated or contraindicated in terms of a net difference in a major endpoint; **and** (ii) evidence that might be reasonably expected to influence materially the patient management of many clinicians who are already aware of the main results of any other trials. The DMC may also consider recommending stopping or modifying the trial, or part of the trial, if: any issues are identified which might compromise patient safety; the recruitment rate or data quality are unacceptable. The TSC can then decide whether to modify the trial, or to seek additional data. Unless this happens, the TSC, the TMG, the Principal investigators, the study participants and all trial staff (except those who provide the confidential analyses to the DMC) will remain blind to the interim results of the randomised questions.

The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet annually during the recruitment and treatment phases of the trial The DMC will also meet after each cohort has been recruited and DLTs assessed in Phase 1b studies and after the first six adult patients (aged ≥25 years) have been recruited to the frontline treatment randomisations. Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently. An emergency meeting may also be convened if a safety issue is identified.

The DMC will report to the TSC, who will report to the TMG. The TMG will convey the findings of the DMC and TSC to the Coordinating Sponsor and funders, where applicable.

31.6 Finance

This is an investigator-initiated and investigator-led trial funded by Cancer Research UK in the UK. In addition, Bayer will be providing funding and free regorafenib for all countries and sites in CT3, the relapse question. Data will be provided to Bayer for regulatory filing purposes.
No payment will be made directly to investigators, patients or other third parties from this funding. Sites will be compensated for their research activities carried out in relation to the trial as defined in the Clinical Study Site Agreement.

For other countries that wish to join the trial, funding will have to be sought by the NCC to adequately support the running of the trial within that country.

31.7 NIHR CRN Portfolio

The FaR-RMS trial is a National Institute for Health Research (NIHR) Clinical Research Network (CRN) Portfolio study (UK).

32. ETHICAL CONSIDERATIONS

The accepted basis for the conduct of clinical trials in humans is founded on the protection of human rights and the dignity of human beings with regard to the application of biology and medicine, and requires compliance with the principles of GCP and detailed guidelines in line with those principles (Directive 2001/20/EC (2) and Directive 2005/28/EC (1)).

GCP is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with GCP provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible (Article 1 (2) of Directive 2001/20/EC).

The NCCs and Investigators shall consider all relevant guidance with respect to commencing and conducting a clinical trial (Article 4 of Directive 2005/28/EC).

The conduct of the trial shall be based on the following international ethical and statutory sources:

- The **WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects**
- If the region has adopted the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: **Convention on Human Rights and Biomedicine** (CETS No.: 164)
- **Directive 2001/20/EC** of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Official Journal L21, 01/05/2001 P. 0034 – 0044) and detailed guidance
- **Directive 2005/28/EC** of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (Official Journal L 91, 09/04/2005 P. 0013 – 0019)
- **Regulation (EU) 2016/679** of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data. Scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use, as agreed upon by the CHMP and published by the Agency, as well as the other pharmaceutical Community guidelines published by the Commission in the different volumes of the rules governing medicinal products in the European Community (Directive 2005/28/EC (9)).

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local site specific approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

33. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the relevant data protection legislation in each country. Patients will be identified using only their unique trial number in correspondence between an NCC and participating sites in its co*untry.* However, if local regulation/guidance permits, patients are asked to give permission for the *applicable NCC* to be sent a copy of their signed ICF which will not be anonymised. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to the applicable NCC (e.g. patient identification logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The NCCs will maintain the confidentiality of all patients' data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer. Representatives of the FaR-RMS trial research team may be required to have access to patients' medical records for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

34. INSURANCE AND INDEMNITY

The Coordinating Sponsor will obtain adequate insurance to cover negligent harm arising from the design of the protocol and its liabilities in relation to the trial.

The NCCs are responsible for obtaining insurance to set up and run the FaR-RMS trial in their respective countries and for ensuring that sites in their country are adequately covered.

University of Birmingham employees are indemnified by the University insurers caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

The University of Birmingham is independent of any pharmaceutical company and, as such, it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

35. PUBLICATION POLICY

Results of this trial will be submitted for publication in peer reviewed journals. The manuscripts will be prepared by the TMG and authorship will be determined by mutual agreement.

The first publications of the main results of this study shall be made as joint multi-centre publications under the lead of the Sponsor (UK Coordinating Centre at the CRCTU) and the Chief Investigator. Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication to allow time for review, resolution of any outstanding issues and approval. Authors must acknowledge that the trial was performed with the support of the University of Birmingham and, where applicable, other NCCs. Intellectual property rights will be addressed in the agreements between the NCCs and in the clinical study site agreement (or country specific equivalent) between the NCCs and sites.

Individual NCCs will be allowed to publish their results. However, the publication of outcome results from the whole trial must precede efficacy result publications from individual countries, unless the TMG decides otherwise.

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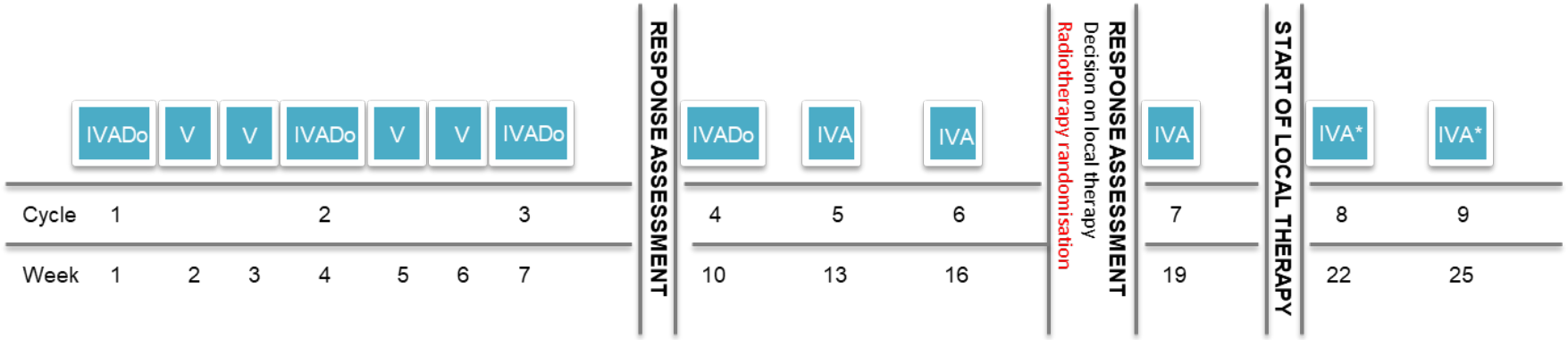
APPENDIX 1. CHEMOTHERAPY FLOW CHARTS

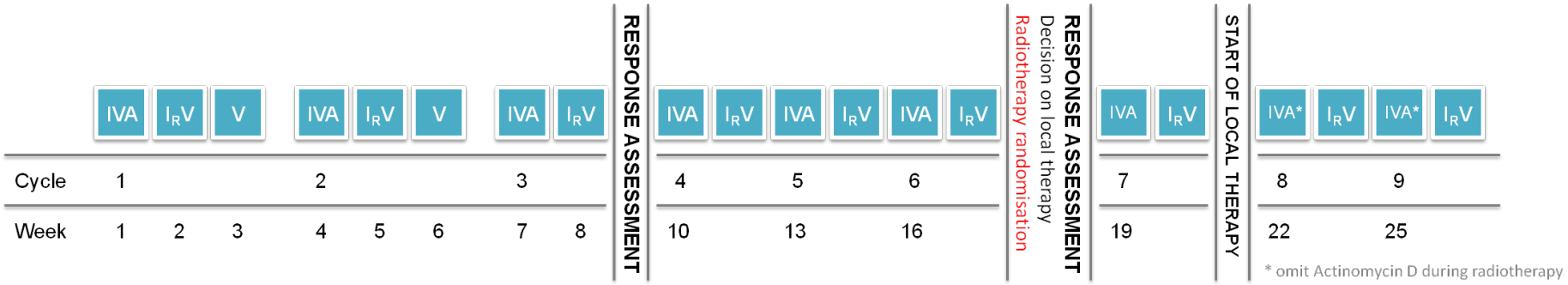
I. INDUCTION: VHR (SUBGROUP H)

IVADo



* omit Actinomycin D during radiotherapy

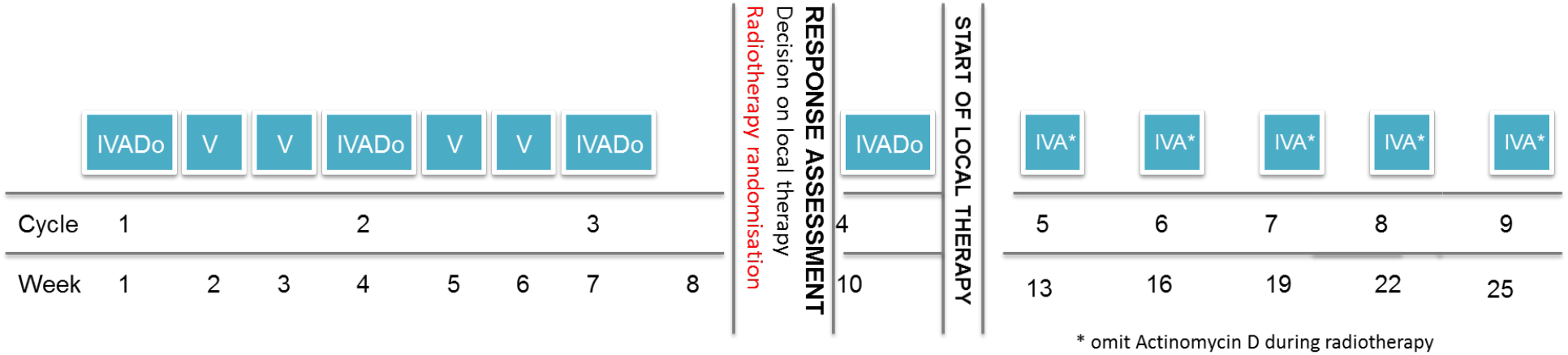
I_RIVA



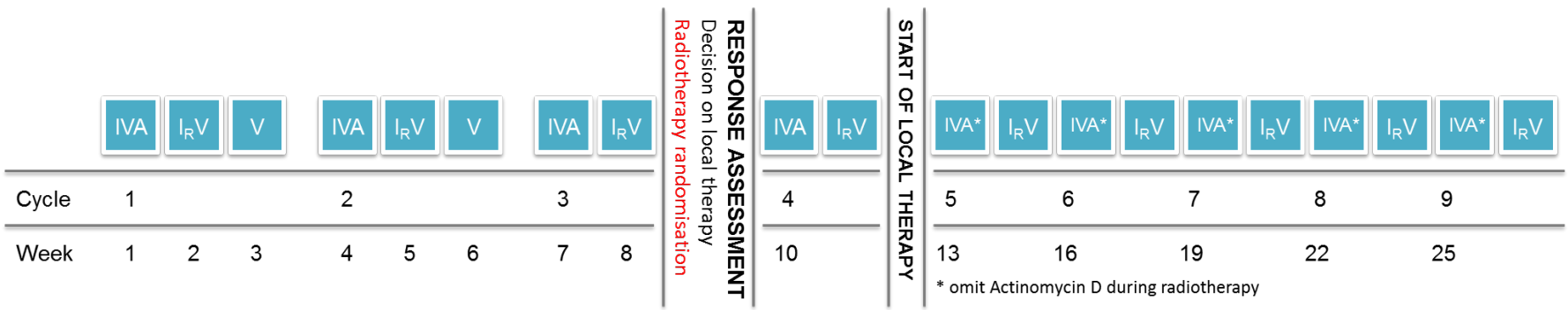
* omit Actinomycin D during radiotherapy

II. INDUCTION: VHR (SUBGROUP G)

IVADo

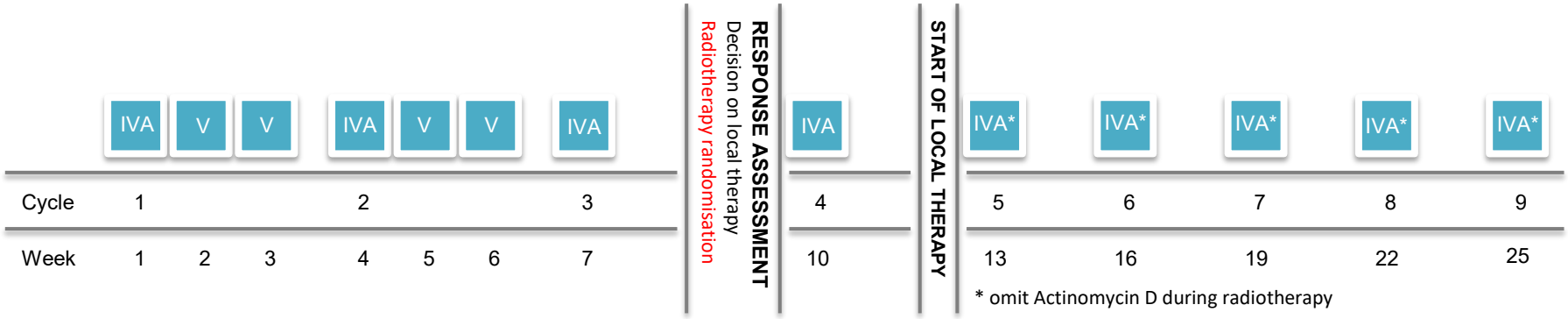


IRIVA

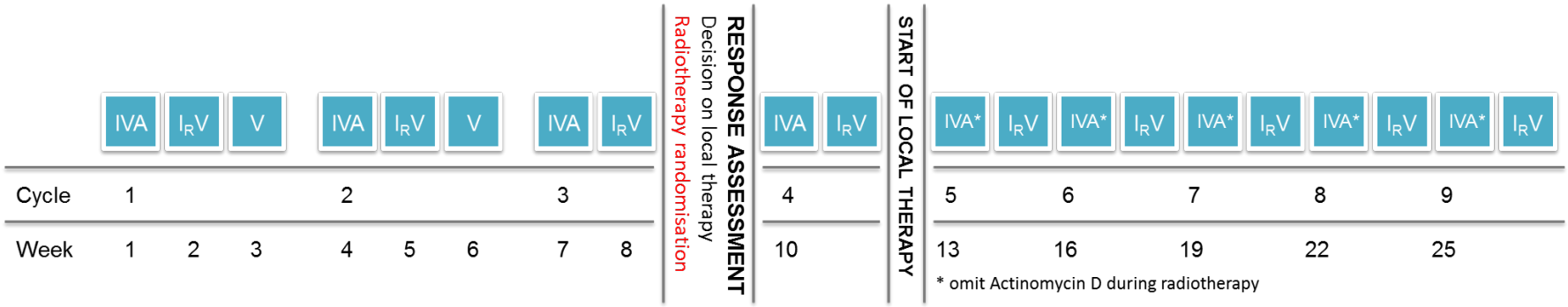


III. INDUCTION: HR (SUBGROUP D,E,F)

IVA

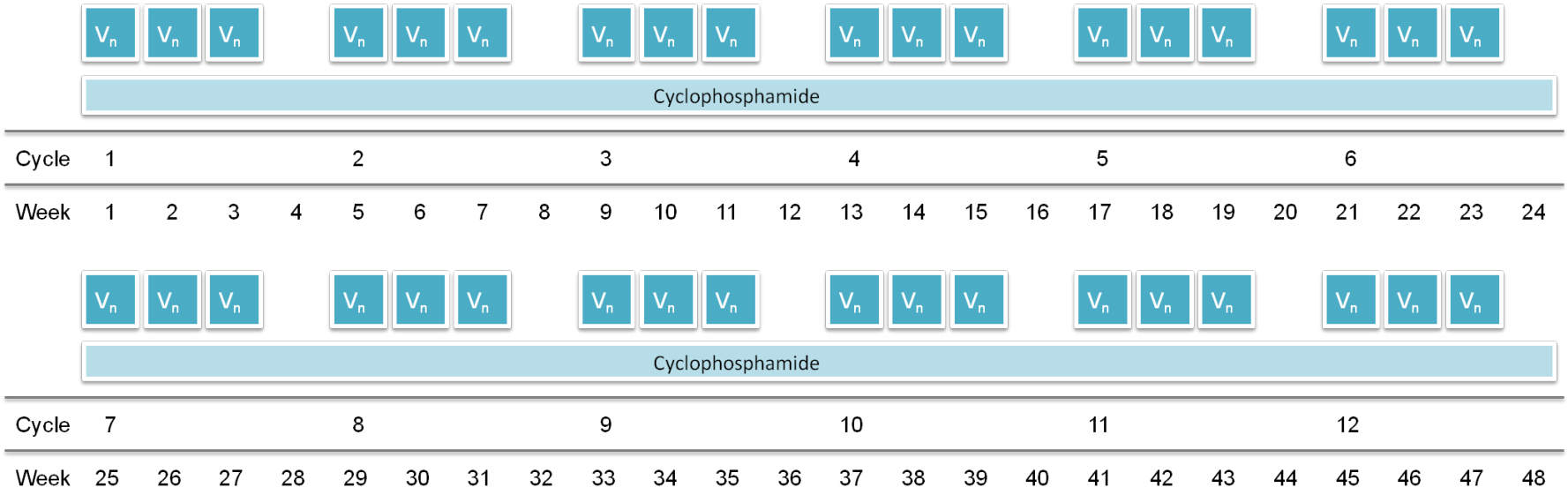


IRIVA


IVA
IRV
V
IVA
IRV
V
IVA
IRV
RESPONSE ASSESSMENT
Decision on local therapy
Radiotherapy randomisation
IVA
IRV
START OF LOCAL THERAPY
IVA*
IRV
IVA*
IRV
IVA*
IRV
IVA*
IRV
IVA*
IRV
Cycle 1 2 3 4 5 6 7 8 9
Week 1 2 3 4 5 6 7 8 10 13 16 19 22 25
* omit Actinomycin D during radiotherapy

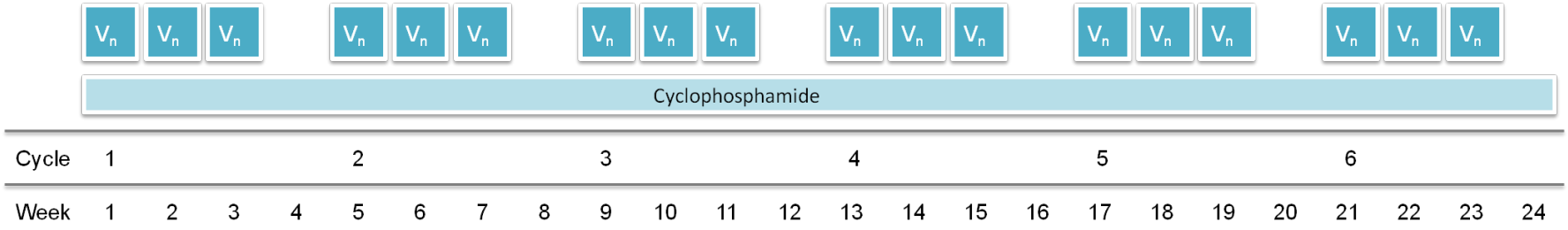
IV. MAINTENANCE: VHR (SUBGROUPS H, G)

Oral and i.v. vinorelbine (Vn)



Repeat for a further 12 cycles if patient is randomised to continue treatment

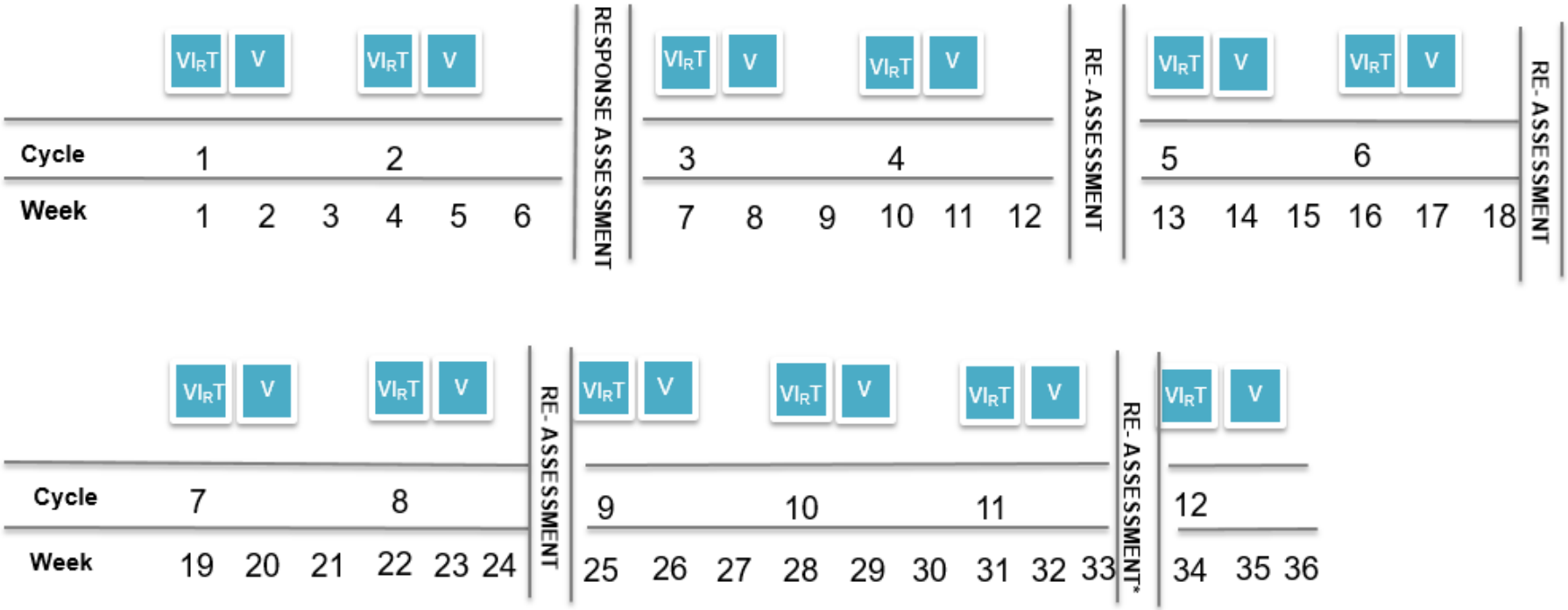
V. MAINTENANCE: HR (SUBGROUPS D,E,F)



Repeat for a further 6 cycles if patient is randomised to continue treatment

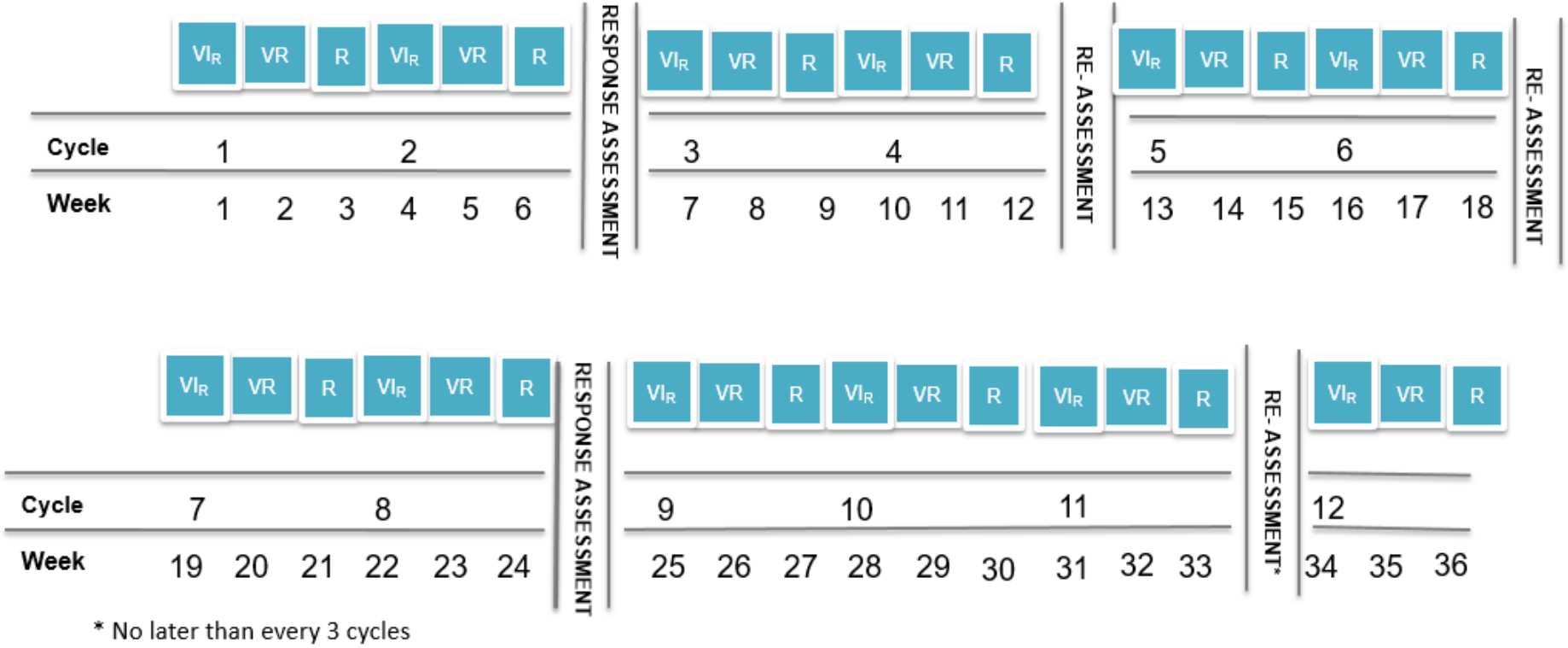
VI. RELAPSE

VIRT



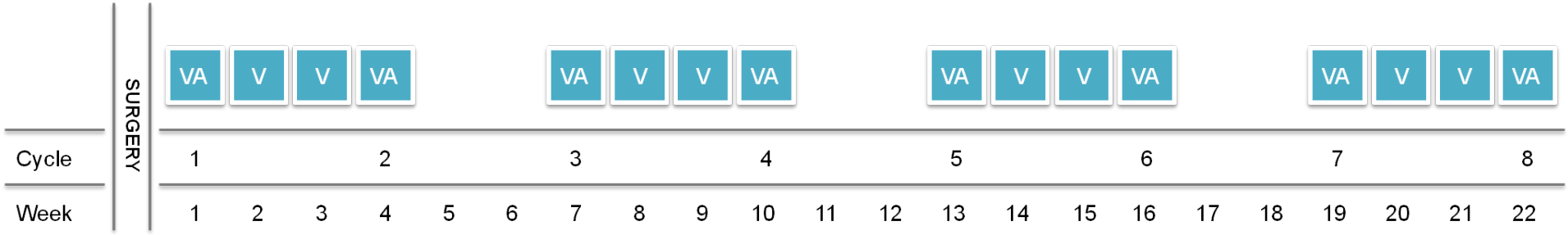
* No later than every 3 cycles

VI_RR



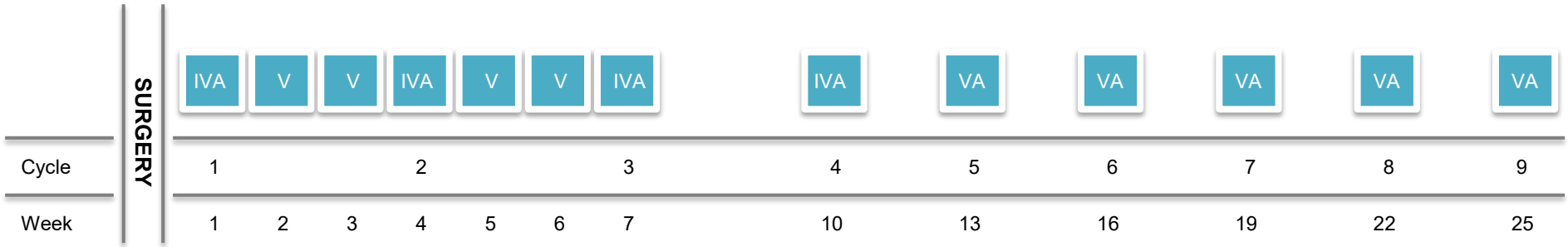
APPENDIX 2. LOW & STANDARD RISK INDUCTION CHEMOTHERAPY GUIDELINES

I. SUBGROUP A



II. SUBGROUP B

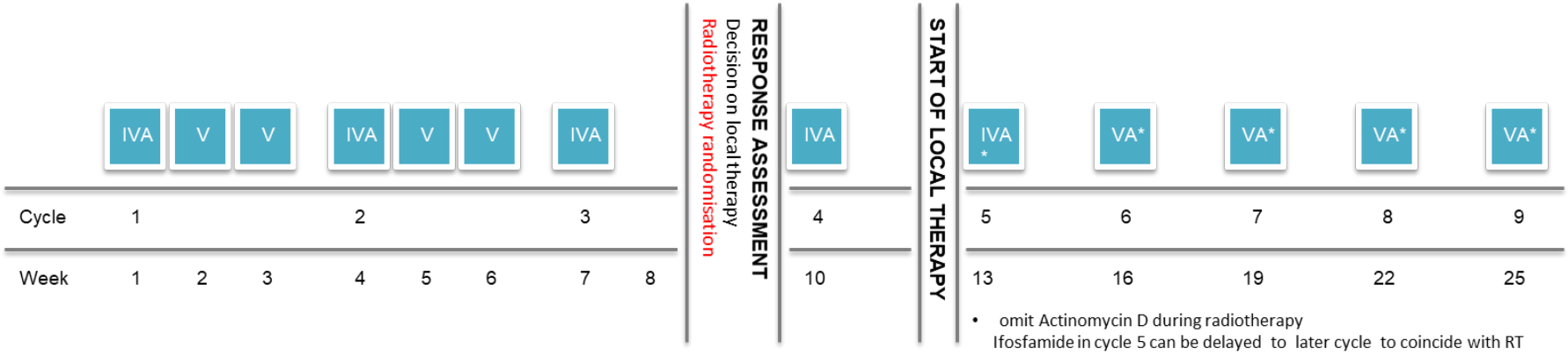
iii. Note: Some patients with age > 10 with paratesticular RMS (particularly those with > 5 cm tumour) may be at risk of a poorer outcome and may benefit from more detailed staging with retroperitoneal lymph node (RPLN) sampling and more intensive, risk-adapted chemotherapy. The current recommendation is to perform RPLN staging for PTRMS > 10 years. If this is not feasible for any reason, the patient should be upstaged and treated with 9 courses of IVA



IV. SUBGROUP C

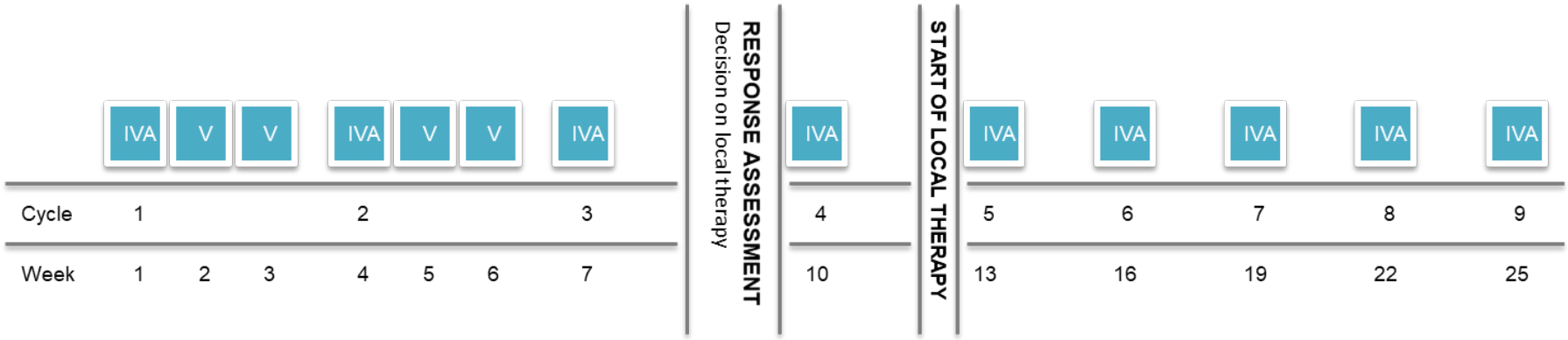
v. **Note: Bladder-Prostate primary tumours** are now regarded favourable site based on favourable outcome in RMS2005 where these were treated according to the High Risk regimen. Based on their favourable outcome the TMG decided these should not be subject to High Risk randomisations but ALL should receive 9xIVA chemotherapy. **This means ALL Bladder-Prostate primaries should receive 9 x IVA irrespective of receiving radiotherapy.**

Radiotherapy



No

No radiotherapy


IVA
V
V
IVA
V
V
IVA
IVA
IVA
IVA
IVA
IVA
IVA
RESPONSE ASSESSMENT
Decision on local therapy
START OF LOCAL THERAPY
Cycle 1 2 3 4 5 6 7 8 9
Week 1 2 3 4 5 6 7 10 13 16 19 22 25

APPENDIX 3. DOSE MODIFICATIONS FOR INFANTS < 6 MONTHS AND/OR < 8 KG

For infants 3-6 months and/or less than 8 kg: doses calculated by weight with further 33% reduction at least for the two first chemotherapy cycles. If no significant chemotherapy-induced toxicity, progressive increased dose up to full dose by weight may be administered for the next chemotherapy cycles.

For infants < 3 months and/or less than 5 kg: dose calculated by weight with further 50% reduction at least for the two first chemotherapy cycles. If no significant chemotherapy-induced toxicity, progressive increased doses by weight may be administered for the next chemotherapy cycles.

If there is an age change during treatment, use the new appropriate age dosing in the next cycle.

Doxorubicin should be omitted < 3 months

Ifosfamide should be omitted < 3 months

For all infants and the very young ones in particular (< 3 months and/or less than 5 kg), clinicians should pay specific attention to Actinomycin D toxicity and risk of hepatic veno-occlusive disease. At least for the first month of life, vincristine alone may be administered with progressive introduction of actinomycin D and cyclophosphamide with recommended age dose adaptation.

Consult a Clinical Coordinator in the case of a patient <8Kg in the relapsed study (CT3)

APPENDIX 4. DOSE MODIFICATIONS FOR INFANTS 6-12 MONTHS AND/OR < 10 KG

IVADo

6-12 months and/or < 10 kg	**21 day cycle. 9 cycles in total**		
		Daily dose	
Ifosfamide	Days 1 & 2	100 mg/kg	As an i.v infusion (timing as per local practice recommended over 3 hours), with mesna and hydration given according to institutional practice.
Vincristine	Days 1, 8 & 15 (Cycles 1 & 2 ONLY).	0.05 mg/kg	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Vincristine	Day 1 in Cycle 3,4,5,6,7,8 &9	0.05 mg/kg	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Actinomycin D **should be omitted during and for 2 weeks after delivery of radiotherapy**	Day 1.	0.05 mg/kg	As per local practice: recommended as an i.v bolus injection Maximum dose: 2mg.
Doxorubicin **should not be given concomitantly with radiotherapy**	Days 1 & 2 Cycles 1,2,3 and 4 only	1 mg/kg	As an i.v infusion, timing as per local practice: recommended over 1 hour

Substitution

Cyclophosphamide	Day 1	50 mg/kg	As an i.v infusion, timing as per local practice: recommended over 1 hour, with mesna and hydration given according to institutional practice
Cyclophosphamide may replace ifosfamide in patients with clinical indications such as significant renal dysfunction.			

I_RIVA

6-12 months and/or < 10 kg	**21 day cycle. 9 cycles in total**		
Irinotecan	Days 8,9,10,11 &12	1.7 mg/kg	As an i.v infusion, timing as per local practice: recommended over 1 hour

Ifosfamide	Days 1 & 2	100 mg/kg	As an i.v infusion, timing as per local practice: recommended over 3 hours, with mesna and hydration given according to institutional practice.
Vincristine	Days 1, 8 & 15 (Cycles 1 & 2 ONLY).	0.05 mg/kg	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Vincristine	Day 1 & 8 in (Cycle 3,4,5,6,7,8,9).	0.05 mg/kg	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Actinomycin D **should be omitted during and for 2 weeks after delivery of radiotherapy**	Day 1.	0.05 mg/kg	As per local practice: recommended as an i.v bolus injection Maximum dose: 2mg.
Cefixime* or equivalent	Day 6 to Day 14	by mouth	Recommended (but not mandated) for prophylaxis of irinotecan-induced diarrhoea. .

Substitution

Cyclophosphamide	Day 1	50 mg/kg	As an i.v infusion, timing as per local practice: recommended over 1 hour, with mesna and hydration given according to institutional practice
Cyclophosphamide may replace ifosfamide in patients with clinical indications such as significant renal dysfunction			

*for cefixime recommended dose is 8mg/kg once daily by mouth, maximum dose: 400mg

IVA

6-12 months and/or < 10 kg	**21 day cycle. 9 cycles in total**		
		Daily dose	
Ifosfamide	Days 1 & 2	100 mg/kg	As an i.v infusion, timing as per local practice: recommended over 3 hours, with mesna and hydration given according to institutional practice.
Vincristine	Days 1, 8 & 15 (Cycles 1 & 2 ONLY).	0.05 mg/kg	As per local practice: recommended asa short infusion Maximum dose: 2mg.
Vincristine	Day 1 in Cycle 3,4,5,6,7,8 &9	0.05 mg/kg	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Actinomycin D **should be omitted during and for 2 weeks after delivery of radiotherapy**	Day 1.	0.05 mg/kg	As per local practice: recommended as an i.v bolus injection Maximum dose: 2mg.

Substitution

Cyclophosphamide	Day 1	50 mg/kg	As an i.v infusion , timing as per local practice: recommended over 1 hour, with mesna and hydration given according to institutional practice
Cyclophosphamide may replace ifosfamide in patients with clinical indications such as significant renal dysfunction			

VI$_R$T

6-12 months and/or < 10 kg	**21 day intervals. Up to 12 cycles**		
		Daily dose	
Vincristine	Days 1 & 8.	0.05mg/kg	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Irinotecan	Days 1,2,3,4&5	1.7 mg/kg	As an i.v infusion over 1 hour
Temozolomide	Days 1,2,3,4&5	4.2 mg/kg	Oral. Prior to vincristine and irinotecan. Escalate to 5mg/kg/day in Cycle 2 if no toxicity > grade 3
	Temozolomide: The starting dose will be 4.2 mg/kg/day. The dose of will be escalated to 5 mg/kg/day at cycle 2 for patients who do not experience ≥ grade 3 toxicity of any kind. The dose should be rounded to the nearest 5 mg.		

Cefixime* or equivalent	Day 6 to Day 14	by mouth	Recommended (but not mandated) for prophylaxis of irinotecan-induced diarrhoea.

*for cefixime recommended dose is 8mg/kg once daily by mouth, maximum dose: 400mg

VI$_R$R

6-12 months and/or < 10 kg	**21 day intervals. Up to 12 cycles**		
		Daily dose	
Vincristine	Days 1 & 8.	0.05mg/kg	As per local practice: recommended as a short infusion Maximum dose: 2mg.
Irinotecan	Days 1,2,3,4&5	1.7 mg/kg	As an i.v infusion over 1 hour
Regorafenib	See section 11.2.4		
Cefixime* or equivalent	Day 6 to Day 14	by mouth	Recommended (but not mandated) for prophylaxis of irinotecan-induced diarrhoea.

***FOR CEFIXIME RECOMMENDED DOSE IS 8MG/KG ONCE DAILY BY MOUTH, MAXIMUM DOSE: 400MG**

APPENDIX 5. ORAL VINORELBINE DOSING CHART

		Number of capsules				
BSA	Calculated dose (60mg/m^2)	20mg.	30mg.	80mg.	Dose administered (mg.)	Difference
0.5	30		1		30	0%
0.55	33		1		30	-9%
0.6	36	2			40	11%
0.65	39	2			40	3%
0.7	42	2			40	-5%
0.75	45	1	1		50	11%
0.8	48	1	1		50	4%
0.85	51	1	1		50	-2%
0.9	54	1	1		50	-7%
0.95	57		2		60	5%
1	60		2		60	0%
1.05	63		2		60	-5%
1.1	66	2	1		70	6%
1.15	69	2	1		70	1%
1.2	72	2	1		70	-3%
1.25	75			1	80	7%
1.3	78			1	80	3%
1.35	81			1	80	-1%
1.4	84			1	80	-5%
1.45	87		3		90	3%
1.5	90		3		90	0%
1.55	93		3		90	-3%
1.6	96	1		1	100	4%
1.65	99	1		1	100	1%
1.7	102	1		1	100	-2%
1.75	105	1		1	100	-5%
1.8	108		1	1	110	2%
1.85	111		1	1	110	-1%
1.9	114		1	1	110	-4%
1.95	117	2		1	120	3%
2	120	2		1	120	0%

APPENDIX 6. ORAL CYCLOPHOSPHAMIDE DOSING CHART

Supplied as 50mg tablets

BSA	Daily dose (mg.)	Total weekly dose (mg.)	Dose schedule (1 50mg tablet each day)	Number of 50mg tablets/week	Dose difference from calculated
0.50	12.5	87.5	Mon & Thur	2	14%
0.55	13.75	96.25	Mon & Thur	2	4%
0.60	15	105	Mon & Thur	2	-5%
0.65	16.25	113.75	Mon & Thur	2	-12%
0.70	17.5	122.5	Mon & Thur	2	-18%
0.75	18.75	131.25	Mon, Wed & Fri	3	14%
0.80	20	140	Mon, Wed & Fri	3	7%
0.85	21.25	148.75	Mon, Wed & Fri	3	1%
0.90	22.5	157.5	Mon, Wed & Fri	3	-5%
0.95	23.75	166.25	Mon, Wed & Fri	3	-10%
1.00	25	175	Mon, Wed, Fri, & Sun	4	14%
1.05	26.25	183.75	Mon, Wed, Fri, & Sun	4	9%
1.10	27.5	192.5	Mon, Wed, Fri, & Sun	4	4%
1.15	28.75	201.25	Mon, Wed, Fri, & Sun	4	-1%
1.20	30	210	Mon, Wed, Fri, & Sun	4	-5%
1.25	31.25	218.75	Mon, Wed, Fri, & Sun	4	-9%
1.30	32.5	227.5	Mon, Wed, Fri, Sat & Sun’	5	10%
1.35	33.75	236.25	Mon, Wed, Fri, Sat & Sun	5	6%
1.40	35	245	Mon, Wed, Fri, Sat & Sun	5	2%
1.45	36.25	253.75	Mon, Wed, Fri, Sat & Sun	5	-1%
1.50	37.5	262.5	Mon, Wed, Fri, Sat & Sun	5	-5%
1.55	38.75	271.25	Mon, Wed, Fri, Sat & Sun	5	-8%

1.60	40	280	Mon, Wed, Thur, Fri, Sat & Sun	6	7%
1.65	41.25	288.75	Mon, Wed, Thur, Fri, Sat & Sun	6	4%
1.70	42.5	297.5	Mon, Wed, Thur, Fri, Sat & Sun	6	1%
1.75	43.75	306.25	Mon, Wed, Thur, Fri, Sat & Sun	6	-2%
1.80	45	315	Mon, Wed, Thur, Fri, Sat & Sun	6	-5%
1.85	46.25	323.75	Mon, Wed, Thur, Fri, Sat & Sun	6	-7%
1.90	47.5	332.5	Daily	7	5%
1.95	48.75	341.25	Daily	7	3%
2.00	50	350	Daily	7	0%

APPENDIX 7. WMA DECLARATION OF HELSINKI

Please refer to www.wma.net/en/20activities/10ethics/10helsinki/index.html

APPENDIX 8. DEFINITION OF ADVERSE EVENTS

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Adverse Reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered.

Comment:

An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the Investigator***

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE 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 unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus, hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms), or for social reasons (e.g. respite care), are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Serious Adverse Reaction (SAR)

An Adverse Reaction which also meets the definition of a Serious Adverse Event.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the Reference Safety Information.

A SUSAR should meet the definition of an AR, UAR and SAR.

Unexpected Adverse Reaction (UAR)

An AR, the nature or severity of which is not consistent with the Reference Safety Information.

When the outcome of an AR is not consistent with the Reference Safety Information the AR should be considered unexpected.

APPENDIX 9. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX 10. CLAVIEN-DINDO SCALE

TABLE 2. Clavien-Dindo Classification of Surgical Complications	
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs such as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade IIIa	Surgical, endoscopic, or radiological intervention that is not under general anesthesia
Grade IIIb	Surgical, endoscopic, or radiological intervention that is under general anesthesia
Grade IVa	Life-threatening complication requiring intermediate care or intensive care unit management, single organ dysfunction (including dialysis, brain hemorrhage, ischemic stroke, and subarrachnoidal bleeding)
Grade IVb	Life-threatening complication requiring intermediate care or intensive care unit management, multi-organ dysfunction (including dialysis)
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication

APPENDIX 11. PERCIST 1.0 CRITERIA [88]

Characteristic	PERCIST 1.0 CRITERIA
Measurability of lesions at baseline	1. Measurable target lesion is hottest single tumor lesion SUL of "maximal 1.2-cm diameter volume ROI in tumor" (SUL peak). SUL peak is at least 1.5-fold greater than liver SUL mean + 2 SDs (in 3-cm spherical ROI in normal right lobe of liver). If liver is abnormal, primary tumor should have uptake > 2.0 × SUL mean of blood pool in 1-cm-diameter ROI in descending thoracic aorta extended over 2-cm z-axis. 2. Tumor with maximal SUL peak is assessed after treatment. Although typically this is in same region of tumor as that with highest SUL peak at baseline, it need not be. 3. Uptake measurements should be made for peak and maximal single-voxel tumor SUL. Other SUV metrics, including SUL mean at 50% or 70% of SUV peak, can be collected as exploratory data; TLG can be collected ideally on basis of voxels more intense than 2 SDs above liver mean SUL (see below) 4. These parameters can be recorded as exploratory data on up to 5 measurable target lesions, typically the 5 hottest lesions, which are typically the largest, and no more than 2 per organ. Tumor size of these lesions can be determined per RECIST 1.1
Normalization of uptake	Normal liver SUL must be within 20% (and <0.3 SUL mean units) for baseline and follow-up study to be assessable. If liver is abnormal, blood-pool SUL must be within 20% (and <0.3 SUL mean units) for baseline and follow-up study to be assessable. Uptake time of baseline study and follow-up study 2 must be within 15 min of each other to be assessable. Typically, these are at mean of 60 min after injection but no less than 50 min after injection. Same scanner, or same scanner model at same site, injected dose, acquisition protocol (2- vs. 3-dimensional), and software for reconstruction, should be used. Scanners should provide reproducible data and be properly calibrated
Objective response	CMR: complete resolution of 18F-FDG uptake within measurable target lesion so that it is less than mean liver activity and indistinguishable from surrounding background blood-pool levels. Disappearance of all other lesions to background blood-pool levels. Percentage decline in SUL should be recorded from measurable region, as well as (ideally) time in weeks after treatment was begun (i.e., CMR −90, 4). No new 18F-FDG-avid lesions in pattern typical of cancer. If progression by RECIST, must verify with follow-up.

	PMR: reduction of minimum of 30% in target measurable tumor 18F-FDG SUL peak. Absolute drop in SUL must be at least 0.8 SUL units, as well. Measurement is commonly in same lesion as baseline but can be another lesion if that lesion was previously present and is the most active lesion after treatment. ROI does not have to be in precisely same area as baseline scan, though typically it is. No increase, >30% in SUL or size of target or nontarget lesions (i.e., no PD by RECIST or IWC) (if PD anatomically, must verify with follow-up). Reduction in extent of tumor 18F-FDG uptake is not requirement for PMR. Percentage decline in SUL should be recorded, as well as (ideally) time in weeks after treatment was begun (i.e., PMR −40, 3). No new lesions. SMD: not CMR, PMR, or PMD. SUL peak in metabolic target lesion should be recorded, as well as (ideally) time from start of most recent therapy, in weeks (i.e., SMD −15, 7). PMD: >30% increase in 18F-FDG SUL peak, with >0.8 SUL unit increase in tumor SUV peak from baseline scan in pattern typical of tumor and not of infection/treatment effect. OR: Visible increase in extent of 18F-FDG tumor uptake (75% in TLG volume with no decline in SUL. OR: New 18F-FDG-avid lesions that are typical of cancer and not related to treatment effect or infection. PMD other than new visceral lesions should be confirmed on follow-up study within 1 mo unless PMD also is clearly associated with progressive disease by RECIST 1.1. PMD should be reported to include percentage change in SUV peak, (ideally, time after treatment, in weeks) and whether new lesions are present/absent and their number (i.e., PMD, +35, 4, new: 5). Because SUL is continuous variable, dividing response criteria into limited number of somewhat arbitrary response categories loses much data. For this reason, PERCIST preserves percentage declines in SUV peak in each reported category. Because rapidity with which scan normalizes is important (faster appears better), PERCIST asks for time from start of treatment as part of reporting. For example, CMR 90, 1, is probably superior to CMR 90, 10, especially if latter patient were SMD 20, 1. More than one measurement of PET response may be needed at differing times, and it may be treatment type–dependent. PERCIST 1.0 evaluates SUL peak of only hottest tumor. This is possible limitation of approach, but lesions and their responses are highly correlated in general. Additional data are required to determine how many lesions should be assessed over 1. A suggested option is to include the 5 hottest lesions, or the 5 observed on RECIST 1.1 that are most measurable. Percentage change in SUL can be reported for single lesion with largest increase in uptake or smallest decline in uptake. Additional studies will be needed to define how many lesions are optimal for assessment

	Nontarget lesions: CMR, disappearance of all 18F-FDG–avid lesions: PMD, unequivocal progression of 18F-FDG–avid nontarget lesions or appearance of new 18F-FDG–avid lesions typical of cancer; non-PMD: persistence of one or more nontarget lesions or tumor markers above normal limits.
Overall Response	Best response recorded in measurable disease from treatment start to disease progression or recurrence Non-PMD in measurable or nonmeasurable nontarget lesions will reduce CR in target lesion to overall PMR. Non-PMD in nontarget lesions will not reduce PR in target lesions
Duration of Response	1. Overall CMR: from date CMR criteria are first met; to date recurrent disease is first noted. 2. Overall response: from date CMR or PMR criteria are first met (whichever status came first); to date recurrent disease is first noted. 3. SMD: from date of treatment start to date PMD is first noted.

TLG = total lesion glycolysis; CMR = complete metabolic response; PMR = partial metabolic response; PD = progressive disease; SMD = stable metabolic disease; PMD = progressive metabolic disease; CR = complete remission; PR = partial remission; NC = no change. SUL= standardized uptake value lean

For PERCIST: Single-voxel SUL is commonly used but has been reported to be less reproducible than SUL peak, especially with very small single-voxel values. It is suggested, but not required, that lesions assessed on PERCIST be larger than the 1.5-cm-diameter volume ROI used to minimize partial-volume effects. Percentage changes are proposed to deal with SUL peak changes. Use of maximal SUL could be explored. If 5 lesions are used as exploratory approach, it is suggested that sum of SULs of baseline 5 lesions serve as baseline for study. After treatment, sum of same 5 lesions should be used. Percentage change in SUL is based on change in these sums from study 1 to study 2. Exploratory analysis can include calculating percentage change in SUL in individual lesions and averaging them. This may produce different result. We believe summed SUL approach will be less prone to minor errors in measurements.

For total lesion glycolysis: Exploratory analysis can include either all foci of tumor with maximal SUL > 2 SDs above normal liver, 5 lesions with highest SUL, or lesion with highest SUL. It is suggested that threshold approach, typically at 2 SDs above normal liver SUL, be used to generate lower bounds of ROI (3 SDs could be used for very active tumors). We believe this approach will be less variable than methods based on maximal SUL with percentage of maximal cutoff. Criteria for progression include 75% growth in TLG for SUL and are conservatively placed at 75% increase. Because 20% increase in EORTC linear size scales to 73% volume increase, the figures are comparable. Progression is judged from best response if being assessed after first scan was performed. For response by TLG, we propose 45% reduction as useful starting point, but more data are needed to make firm recommendations. If TLG is determined, explicit methodologic details should be provided. It should not be a primary metric, but a secondary endpoint at this time.

APPENDIX 12. HEALTH RELATED QUALITY OF LIFE

Health-related quality of life assessment within FaR-RMS clinical trial

Rationale

Patients with Rhabdomyosarcoma (RMS), in particular those with high risk disease undergo highly intensive therapies including chemotherapy, surgery and radiotherapy in the attempt to cure their disease. These treatments have several side effects which can lead to significant morbidity and time spent in hospital. This, along with the physical and emotional morbidity associated with the cancer itself is likely to adversely affect health-related quality of life (HRQoL) of both patients and their families. Historically, evaluation of cancer treatments has focused on objective outcomes such as radiological response, progression-free and overall survival, and a healthcare-provider perspective of treatment-related toxicities. More recently, increasing attention has been given to patient reported outcomes (PROs), defined as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else,' in order to evaluate treatment efficacy (www.fda.gov). PROs include a range of outcomes such as symptoms, functioning and HRQoL. HRQoL is the most widely used PRO and is a multidimensional concept that includes the patient's perception of the impact of the disease and its treatment on physical, psychological and social functioning.[89]

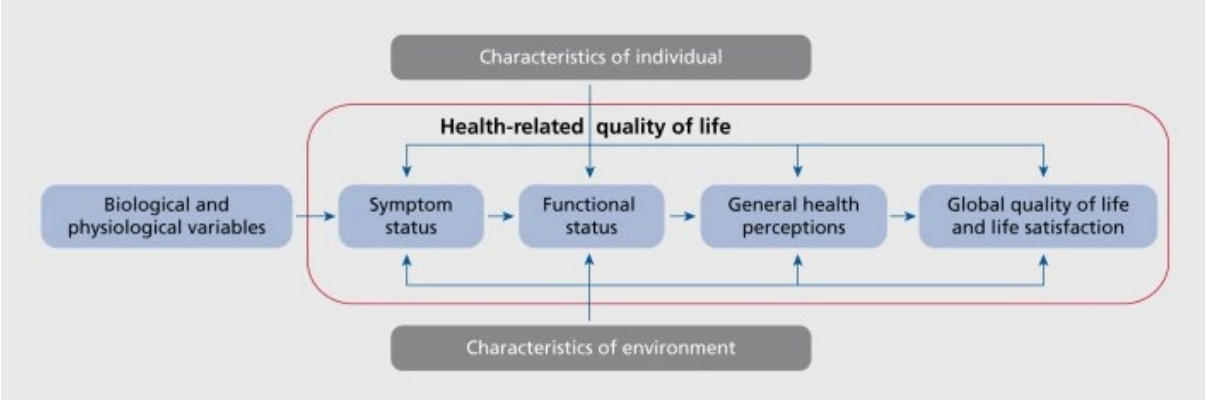
To date there are only a limited number of published studies of HRQoL during treatment for RMS[2,3]. These have focused on particular disease sites or specific treatment modalities such as brachytherapy or proton beam radiotherapy. The large cohort within the FaR-RMS trial presents an opportunity to study HRQoL across a wide range of disease sites and compare HRQoL scores between different treatment strategies.

The FaR-RMS clinical trial comprises a series of research questions relating to chemotherapy and radiotherapy. This is the first study to prospectively randomise timing of radiotherapy in relation to surgery. The primary aim of the study is to improve survival outcomes for all patients. A secondary aim is to study and better understand HRQoL of patients undergoing radiotherapy and identify whether there

are any differences in HRQoL between the different radiotherapy arms of the study. If no difference in survival outcomes or toxicity is seen between different randomisation arms then HRQoL outcomes may be key in determining which treatment strategy to take forward as standard of care.

Background

HRQoL (see below diagram) may be explored in a health context in a number of ways[4]. It can be defined as a) A multidimensional concept that includes subjective reports of symptoms, side effects, functioning in multiple life domains, and general perceptions of life satisfaction and quality[5] or b) The impact of disease and treatment on domains of physical, psychological, and social functioning[6].



There are many HRQoL measures available for the adult population. The FaR-RMS will include children from the age of 6 months as well as adults of all ages. There is no available HRQoL measure which will cover the entire population. In children, attempts to determine HRQoL have included the use of proxy measures, usually completed by a parent or carer, or surrogate measures such as school absence. Reliance on any of these individual measures is limited as none alone will provide a comprehensive or sensitive indicator of overall HRQoL during treatment for RMS. On the other hand the use of multiple measures is cumbersome and they can be lengthy, repetitive and may lack sensitivity to detect the specific impact of cancer on the child's HRQoL. For this reason, a number of specifically developed measures of HRQoL for children with cancer have been developed and reported. The measure chosen for this study for patients up to the age of 18 is the PedsQL™ (Varni[7]) which fulfils the following criteria:

1. Availability of parallel versions, enabling comparisons to be made between parent and child views about HRQoL.

2. Adequate psychometric properties. Varni et al[7] reported that children who had completed treatment had a better HRQoL than those who were still on treatment.
3. Brevity. The PedsQL™ remains one of the most brief and comprehensive measures of HRQoL.
4. Availability of population norms. Varni published norms for the US population and the properties of the measure in the British population have also been published[8]. Comparisons with norms will be made to enable us to distinguish changes in HRQoL which are the result of a cancer diagnosis and treatment compared with any that might be attributable to normal age-related changes.

Within the adult population, one of the biggest challenges in sarcoma is how to assess HRQoL in this heterogeneous patient group. For patients aged 18 years and over the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) will be used. This 30-item HRQoL questionnaire comprises five functional scales (physical, role, cognitive, emotional and social), a global quality of life scale (overall health and overall quality of life during the past week), three symptom scales and a number of single items assessing common symptoms and perceived financial impact of the disease. After linear transformation, all scales and single item measures range in score from 0-100. A higher score on the functional scales and global HRQoL means better functioning and HRQoL, whereas a higher score on the symptom scales means more complaints. Clinical important differences were determined according to the guidelines of the EORTC Quality of Life Group[10]. This size effect as measured by the EORTC QLQ-C30 is divided into four size classes: large (one representing unequivocal clinical relevance), medium (likely to be clinically relevant, but to a lesser extent), small (subtle nevertheless clinically relevant) and trivial (circumstances unlikely to have any clinical relevance or where there was no difference).

Aims

1. To compare the impact of the different radiotherapy regimens in FaR-RMS on HRQoL as follows:
    (i) Pre-operative versus post-operative radiotherapy (RT1[A])

(ii) Radiotherapy to all sites versus limited radiotherapy (patients with widespread metastatic disease) (RT2).

Population

All patients who participate in the radiotherapy randomisations RT1[A] and RT2 will be provided with the appropriate HRQoL questionnaires (where the appropriate language questionnaire is available).

Methods

HRQoL Tools

- For children aged <18 years the PedsQL™ generic and cancer specific versions will be used.
    a. Children aged 8 years and older will be invited to provide a self-report
    b. For children <8 years old a parent proxy report will be used
    c. Parent reports will be collected for all patients aged <16 years

Patients <18 at diagnosis who start completing the PedsQL, should continue to be given the PedsQL at all time points

- For patients aged ≥18 years the EORTC QLQ-C30 will be used.

Time points

The questionnaires will be given to patients at the following time points:

1. Prior to starting radiotherapy
2. At the end of radiotherapy (within 2 weeks)
3. 3 months post radiotherapy (to assess differences between pre-operative and post-operative radiotherapy)
4. 24 months post radiotherapy

Recruitment

The HRQoL study is an integral part of the FaR-RMS trial and patients will be recruited to the study at the time of recruitment to the radiotherapy randomisation. Access to the questionnaires will be given by a member of site staff based on patient eligibility and age at the assessment time point. Parent proxy

questionnaires will be given to those with children aged 0 to 15 years inclusive. Patient questionnaires will be given to all those aged 8 or over. Most will be able to complete these with minimum explanation (time for completion approximately 10 minutes). Site staff will be given specific instructions about administration of questionnaires and ongoing support throughout the running of the study by the HRQoL leads.

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APPENDIX 13. BIOLOGICAL STUDIES ENDPOINTS

To validate whether the use of fusion status (PAX3/PAX7-FOXO1) in place of histopathological diagnosis improves risk stratification.
Currently treatment of patients with RMS is stratified according to age, tumour size ,Histology, IRS post surgical stage and Lymph Node involvement. In FaR-RMS histology will be replaced by assessing use of PAX3/7/FOXO1 rearrangement/and or fusions. This will be the first prospective study were all cases will have fusion status assessed, irrespective of histological subtype and therefore no bias as to testing criteria. Univariate and multivariate analysis looking at Event Free Survival and Overall Survival will be analysed, for both presence of Fusion status and Histological subtyping, comparing fusion positive to fusion negative, compared to ARMS and ERMS and Spindle/Sclerosing RMS.

To determine whether assessment of fusion status is necessary in tumors classified as Embryonal RMS (ERMS) by histopathology
Fusion positive ERMS (PAX3/7/FOXO1) has been described in the literature. However it is not clear what the true incidence of fusions involving these genes is. This gives us the opportunity in a prospective trial to assess fusion status in all histological subtypes of RMS. International review of histology for subtyping will be undertaken to ensure consistency in diagnosis and subtyping. The true incidence of ERMS which are fusion positive will be identified.

To determine whether immunohistochemistry (IHC) assessment for protein expression driven by the fusion protein is an accurate surrogate for fusion status
The use of surrogate markers by immunohistochemistry will be assessed and compared to both Histological subtype and fusion status. This will highlight if PAX3/7/FOXO1 needs to be assessed in all cases of RMS, or if combination of histological subtyping, in conjunction with surrogate markers can identify groups of RMS that does not require testing for presence of rearrangement/fusions involving these genes.

APPENDIX 14. EPSSG GUIDELINES

www.epssgassociation.it

The following guidelines have been produced by the EpSSG:

EpSSG RMS Imaging Guidelines

EpSSG RMS Surgical Guidelines

EpSSG Pathology Guidelines

APPENDIX 15. DW-MRI GUIDELINES

Philips 3 T rhabdomyosarcoma MR template

Head and neck region

INDICATION	PROTOCOL
Soft tissue tumour in the head or neck If possible mark swelling or scar	Before contrast agent administration: sequences 1 to 6 DCE optional
PREPARATION	
Coil	Head / neck
Contrast agent	**Gadolinium** (for instance, Gadovist 0,1 ml per kg body weight)

	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	SURVEY	TFE	MST						
2	T1 TSE	TSE	COR	180 x 180	33	3.0	0.45 x 0.5	15	450 / 700
3	T1 TSE	TSE	TRA	180 x 180	35	3.0	0.6 x 0.66	shortest 15	450 / 750
4	T2 TSE	TSE	COR	180 x 180	33	3.0	0.5 x 0.5	80	2500 / 6000
5	T2 Fat saturation (FS)	MV	TRA	330 x 330	64	3.0	0.8 x 0.8	96	3000 / 4500
6	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map	EPI 2D	TRA	230 x 196	41	3.0	2.0 x 2.0	shortest 75	4000-5000
7	Post-Gd eTHRIVE	TFE	TRA	190 x 190	320	0.9	0.5 x 0.8	shortest 3.2	shortest 6.6
8	Post-Gd T1 TSE DIXON	TSE	TRA	200 x 200	35	3.0	0.6 x 0.78	14	450 / 650
9	Post-Gd T1 TSE DIXON	TSE	COR	180 x 180	33	3.0	0.6 x 0.78	14	450 / 650

Chest and abdomen

1.5 T recommended, see 1.5T protocol.

Extremities

INDICATION	PROTOCOL
Soft tissue tumour arising from the extremities If possible mark swelling or scar	Before contrast agent administration: sequences 1 to 5 During contrast agent administration: sequence 6 After contrast: sequence 7 and 8 with **SPIR**
PREPARATION	
Coil	Posterior and anterior
Contrast agent	**Gadolinium** (for instance, Gadovist 0.1 ml per kg body weight).

	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	SURVEY	FFE	MST						
2	T1 TSE	TSE	TRA	250 x 250	30	4.0	0.8 x 1.1	10	400 / 750
3	T2 TSE mDIXON	TSE	TRA	250 x 250	30	4.0	0.87 x 1.09	80	shortest 2236
4	T1	TSE	SAG/COR	200 x 200	40	3.0	0.8 x 0.9	10	500 / 700

5	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map	EPI	TRA	230 x 230	50	4.0	2.5 x 2.5	shortest 54	4000-5000
6	DCE (start < 20 sec after infusion for fast temporal resolution)	TFE	TRA	300 x 150	8	5..0	1.17 x 2.54	1..5	shortest 6.1
7	Post-Gd T1 TSE SPIR	TSE	SAG/COR	200 x 200	40	3..0	0.8 x 0.9	10	500 / 700
8	Post-Gd T1 TSE SPIR	TSE	TRA	250 x 250	30	4..0	0.8 x 1.1	shortest 10	400 / 750

Philips 1.5T rhabdomyosarcoma MR template

Head and neck

INDICATION	**PROTOCOL**
Soft tissue tumour in the head or neck	Before contrast agent administration: sequences 1 to 6
If possible mark swelling or scar	
PREPARATION	
Coil	Head / neck
Contrast agent	**Gadolinium** (for instance, Gadovist 0.1 ml per kg body weight)

	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	SURVEY	FFE	MST						
2	T1 TSE	TSE	COR	180 x 180	33	3.0	0.6 x 0.74	14	400 / 650
3	T1 TSE	TSE	TRA	180 x 180	35	3.0	0.6 x 0.74	16	400 / 650
4	T2 TSE	TSE	COR	180 x 180	33	3.0	0.45 x 0.5	100	2500 / 3500
5	T2 FS	MV	TRA	330 x 330	64	3.0	1.0 x 1.0	shortest 76	shortest 6063
6	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map	EPI	TRA	200 x 200	41	4.0	2.81 x 2.81	shortest 71	4000-5000
7	Post-Gd eTHRIVE[#]	TFE	TRA	190 x 190	320	1.0	0.8 x 0.9	shortest 4.5	shortest 9.6
8	Post-Gd T1 TSE DIXON[#]	TSE	TRA	180 x 180	35	3.0	0.7 x 0.92	14	400/ 700
9	Post-Gd T1 TSE DIXON[#]	TSE	COR	180 x 180	33	3.0	0.7 x 0.94	14	400 /700

[#] Post-Gd scans should be performed with fat saturation / water excitation.

Chest and abdomen

INDICATION			**PROTOCOL**
Soft tissue tumour in chest or abdomen			Before contrast agent administration: sequences 1 to 11
			After contrast agent administration: repeat sequence 3 and 4 (=sequence 12 and 13)
			Sequence 7 to 11 set around the mass
Urogenital or prostate tumour			Sequence 9 and 10 are mandatory (tT2 TSE and sT2 TSE)
LOCATION TUMOUR	CHEST	First visit	DO NOT ACQUIRE sequences 9 and 10
		Follow up	DO NOT ACQUIRE sequences 9, 10 and 11
	UPPER ABDOMEN	First visit	DO NOT ACQUIRE sequences 9 and 10
		Follow up	DO NOT ACQUIRE sequences 9, 10 and 1

	PELVIC	First visit	ALL SEQUENCES
		Follow up	SELECTION OF SEQUENCE 7, 8, 9 and 10.; NOT sequence 11
PREPARATION			
Coil	Posterior and anterior		
Contrast	**Gadolinium** (for instance, Gadovist 0.1 ml per kg body weight)		

WITH ANESTHESIA (SMALL CHILD)									
	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	SURVEY	FFE	MST						
2	3D T2 TSE with pearbelt	TSE	COR	400 x 353	139	1.15	1.15 x 1.15	90	shortest 455
3	T1 THRIVE 1	TSE	TRA	380 x 331	87	3.0	1.25 x 1.24	shortest 2.9	shortest 6
4	T1 THRIVE 2	TSE	TRA	380 x 331	87	3.0	1.25 x 1.24	shortest 2.9	shortest 6
5	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map 1	EPI	TRA	380 x 332	26	5.0	2.81 x 3.5	shortest 78	4000-5000
6	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map 2	EPI	TRA	380 x 332	26	5.0	2.81 x 3.5	shortest 78	4000-5000
7	T1 TSE	TSE	TRA	250 x 250	65	4.0	0.7 x 0.8	8	400 / 600
8	T2 MV xd FS	TSE	TRA	300 x 300	50	4.0	1 x 1	100	2227
9	T2 TSE*	TSE	SAG	250 x 201	39	4.0	0.65 x 0.92	100	shortest 4029
10	T2 TSE*	TSE	TRA	250 x 250	65	4.0	0.75 x 0.95	100	shortest 6671
11	T1 IN and OUT of phase*	TSE	TRA	300 x 246	25	5.0	1.67 x 2.09	TE1: 2.3/ TE2: 4.3	shortest 6
12	Post-Gd T1 THRIVE 1[#]	TFE	TRA	380 x 331	87	3	1.25 x 1.24	shortest 2.9	shortest 6
13	Post-Gd T1 THRIVE 2[#]	TFE	TRA	380 x 331	87	3.0	1.25 x 1.24	shortest 2.9	shortest 6

*optional

[#] Post-Gd scans should be performed with fat saturation / water excitation.

WITHOUT ANESTHESIA (LARGE CHILD)									
	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	SURVEY	FFE	MST						
2	T2 MV xd	TSE	COR	450 x 450	35	5.0	1 x 1	100	shortest 2457
3	T1 THRIVE 1	TSE	TRA	380 x 299	150	3.0	1.25 x 1.25	shortest 2.9	shortest 6
4	T1 THRIVE 2	TSE	TRA	380 x 299	150	3.0	1.25 x 1.25	shortest 2.9	shortest 6
5	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map 1	EPI	TRA	380 x 380	45	5.0	2.81 x 3.49	shortest 78	4000-5000
6	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map 2	EPI	TRA	380 x 380	45	5.0	2.81 x 3.49	shortest 78	4000-5000
7	T1 TSE	TSE	TRA	250 x 250	65	4.0	0.75 x 0.8	8	400 / 600
8	T2 MV xd FS	TSE	TRA	300 x 300	63	4.0	1 x 1	shortest 57	shortest 2304
9	T2 TSE*	TSE	SAG	250 x 201	39	4.0	0.65 x 0.92	100	shortest 4029
10	T2 TSE*	TSE	TRA	250 x 250	65	4.0	0.75 x 0.95	100	shortest 6671

11	T1 IN and OUT of phase*	TSE	TRA	300 x 246	25	5.0	1.67 x 2.09	TE1:2.3/ TE2:4.3	shortest 163
12	Post-Gd T1 THRIVE 1#	TFE	TRA	380 x 299	150	3	1.25 x 1.25	shortest 2.9	shortest 6
13	Post-Gd T1 THRIVE 2#	TFE	TRA	380 x 299	150	3.0	1.25 x 1.25	shortest 2.9	shortest 6

* optional

Post-Gd scans should be performed with fat saturation / water excitation.

Extremities

INDICATION	**PROTOCOL**
Soft tissue tumour arising from the extremities If possible mark swelling or scar	Before contrast agent administration: sequences 1 to 5 During contrast agent administration: sequence 6 After contrast agent administration: sequence 7 and 8 with **SPIR**
PREPARATION	
Coil	Posterior and anterior
Contrast agent	**Gadolinium** (for instance, Gadovist 0.1 ml per kg body weight)

	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	SURVEY	FFE	MST						
2	T1 TSE	TSE	TRA	200 x 200	29	4.0	0.7 x 0.86	shortest 16	400 / 650
3	T2 TSE mDIXON	TSE	TRA	200 x 200	29	4.0	0.8 x 0.95	80	3500 / 5500
4	T1	TSE	SAG/COR	300 x 300	31	3.0	0.95 x 0.95	15	540 / 650
5	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map	EPI	TRA	200 x 200	40	4.0	2.5 x 2.5	72	4000-5000
6	DCE (start < 20 sec after infusion for fast temporal resolution)	TFE	TRA	200 x 200	8	5.0	1.17 x 2.94	1.3	5.4
7	Post-Gd T1 TSE SPIR#	TSE	SAG/COR	300 x 300	36	3.0	0.95 x 0.9	15	450 / 650
8	Post-Gd T1 TSE SPIR#	TSE	TRA	200 x 200	29	4.0	0.85 x 0.9	20	400 / 650

Post-Gd scans should be performed with fat saturation / water excitation.

Siemens 3 T rhabdomyosarcoma MR template

Head and neck

INDICATION	**PROTOCOL**
Soft tissue tumour in the head or neck If possible mark swelling or scar	Before contrast agent administration: sequences 1 to 6 DCE optional
PREPARATION	
Coil	Head / neck

Contrast agent	**Gadolinium (for instance, Gadovist 0.1 ml per kg body weight)**

	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	SURVEY	TFE	MST						
2	T1 TSE	TSE	COR	180 x 180	33	3	0.45 x 0.5	15	450 / 700
3	T1 TSE	TSE	TRA	180 x 180	35	3	0.6 x 0.66	shortest 15	450 / 750
4	T2 TSE	TSE	COR	180 x 180	33	3	0.5 x 0.5	80	2500 / 6000
5	T2 FS	MV	TRA	330 x 330	64	3	0.8 x 0.8	96	3000 / 4500
7	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map	EPI	TRA	230 x 196	41	3	2.0 x 2.0	shortest 75	4000-5000
8	Post-Gd T1 VIBE	TFE	TRA	190 x 190	320	0.9	0.5 x 0.8	shortest 3.2	shortest 6.6
9	Post-Gd T1 TSE DIXON[#]	TSE	TRA	200 x 200	35	3	0.6 x 0.78	14	450 / 650
10	Post-Gd T1 TSE DIXON[#]	TSE	COR	180 x 180	33	3	0.6 x 0.78	14	450 / 650

[#] Post-Gd scans should be performed with fat saturation / water excitation.

Chest and abdomen

recommended, see 1.5T protocol.

Extremities

INDICATION	**PROTOCOL**
Soft tissue tumour in extremity	Before contrast agent administration: sequences 1 to 4 During contrast agent administration: sequence 7 After contrast agent administration: repeat sequence 2 and 3 with SPIR (=sequence 8 and 9)
If possible mark swelling or scar	

PREPARATION	
Coil	Posterior and anterior
Contrast agent	**Gadolinium (for instance, Gadovist 0.1 ml per kg body weight)**

	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	SURVEY	FFE	MST						
2	T1 TSE	TSE	TRA	250 x 250	30	4	0.8 x 1.1	10	400 / 750
3	T2 TSE mDIXON or T2 SPAIR	TSE	TRA	250 x 250	30	4	0.87 x 1.09	80	shortest 2236
4	T1 TSE	TSE	SAG/COR	200 x 200	40	3	0.8 x 0.9	10	500 / 700
5	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map	EPI	TRA	230 x 230	50	4	2.5 x 2.5	shortest 54	4000-5000
6	DCE (start < 20 sec after infusion for fast temporal resolution)	TFE	TRA	300 x 150	8	5	1.17 x 2.54	1.5	shortest 6.1
7	Post-Gd T1 TSE SPAIR[#]	TSE	SAG/COR	200 x 200	40	3	0.8 x 0.9	10	500 / 700
8	Post-Gd T1 TSE SPAIR[#]	TSE	TRA	250 x 250	30	4	0.8 x 1.1	shortest 10	400 / 750

[#] Post-Gd scans should be performed with fat saturation / water excitation.

Siemens 1.5 T rhabdomyosarcoma MR template

Head and neck

INDICATION	PROTOCOL
Soft tissue tumour in the head or neck If possible mark swelling or scar	Before contrast agent administration: sequences 1 to 6 DCE optional

PREPARATION	
Coil	Head / neck
Contrast agent	**Gadolinium (for instance, Gadovist 0.1 ml per kg body weight)**

	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	SURVEY	FFE	MST						
2	T1 TSE	TSE	COR	180 x 180	33	3	0.6 x 0.74	14	400 / 650
3	T1 TSE	TSE	TRA	180 x 180	35	3	0.6 x 0.74	16	400 / 650
4	T2 TSE	TSE	COR	180 x 180	33	3	0.45 x 0.5	100	2500 / 3500
5	T2 FS	MV	TRA	330 x 330	64	3	1.0 x 1.0	shortest 76	shortest 6063
6	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map	EPI	TRA	200 x 200	41	4	2.81 x 2.81	shortest 71	4000-5000
7	Post-Gd VIBE#	TFE	TRA	190 x 190	320	1	0.8 x 0.9	shortest 4.5	shortest 9.6
8	Post-Gd T1 TSE DIXON#	TSE	TRA	180 x 180	35	3	0.7 x 0.92	14	400 / 700
9	Post-Gd T1 TSE DIXON#	TSE	COR	180 x 180	33	3	0.7 x 0.94	14	400 / 700

Post-Gd scans should be performed with fat saturation / water excitation.

Chest and abdomen

INDICATION		PROTOCOL	
Soft tissue tumour in chest or abdomen		Before contrast agent administration: sequences 1 to 11	
		After contrast agent administration: repeat sequence 3 and 4 (=sequence 12 and 13)	
		Sequence 7 to 11 set around the mass	
Urogenital or prostate tumour		Sequence 9 and 10 are mandatory (tT2 TSE and sT2 TSE)	
LOCATION TUMOUR	CHEST	First visit	DO NOT ACQUIRE sequence 9 and 10
		Follow up	DO NOT ACQUIRE sequence 9, 10 and 11
	UPPER ABDOMEN	First visit	DO NOT ACQUIRE sequence 9 and 10
		Follow up	DO NOT ACQUIRE sequence 9, 10 and 11
	PELVIC	First visit	ALL SEQUENCES
		Follow up	SELECTION OF SEQUENCE 7, 8, 9 and 10. NOT 11
PREPARATION			

Coil	Posterior and anterior
Contrast agent	**Gadolinium (for instance, Gadovist 0.1 ml per kg body weight)**

WITH ANESTHESIA (SMALL CHILD)								
	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	TE [ms]	TR [ms]
1	SURVEY	FFE	MST					
2	3D T2 TSE respiratory triggering	TSE	COR	400 x 353	139	1.15	90	shortest 455
3	T1 VIBE 1	TSE	TRA	380 x 331	87	3	shortest 2.9	shortest 6
4	T1 VIBE 2	TSE	TRA	380 x 331	87	3	shortest 2.9	shortest 6
5	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map 1	EPI	TRA	380 x 332	26	5	shortest 78	4000-5000
6	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map 2	EPI	TRA	380 x 332	26	5	shortest 78	4000-5000
7	T1 TSE	TSE	TRA	250 x 250	65	4	8	400 / 600
8	T2 BLADE FS	TSE	TRA	300 x 300	50	4	100	2227
9	T2 TSE*	TSE	SAG	250 x 201	39	4	100	shortest 4029
10	T2 TSE*	TSE	TRA	250 x 250	65	4	100	shortest 6671
11	T1 IN and OUT of phase*	TSE	TRA	300 x 246	25	5	TE1: 2.3/ TE2: 4.3	shortest 6
12	Post-Gd T1 VIBE 1#	TFE	TRA	380 x 331	87	3	shortest 2.9	shortest 6
13	Post-Gd T1 VIBE 2#	TFE	TRA	380 x 331	87	3	shortest 2.9	shortest 6
	*optional							

WITHOUT ANESTHESIA (LARGE CHILD)								
	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	TE [ms]	TR [ms]
1	SURVEY	FFE	MST					
2	T2 BLADE xd	TSE	COR	450 x 450	35	5	100	shortest 2457
3	T1 VIBE 1	TSE	TRA	380 x 299	150	3	shortest 2.9	shortest 6
4	T1 VIBE 2	TSE	TRA	380 x 299	150	3	shortest 2.9	shortest 6
5	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map 1	EPI	TRA	380 x 380	45	5	shortest 78	4000-5000
6	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map 2	EPI	TRA	380 x 380	45	5	shortest 78	4000-5000
7	T1 TSE	TSE	TRA	250 x 250	65	4	8	400/600
8	T2 BLADE FS	TSE	TRA	300 x 300	63	4	shortest 57	shortest 2304
9	T2 TSE*	TSE	SAG	250 x 201	39	4	100	shortest 4029

10	T2 TSE*	TSE	TRA	250 x 250	65	4	100	shortest 6671
11	T1 IN and OUT of phase*	TSE	TRA	300 x 246	25	5	TE1: 2.3/ TE2: 4.3	shortest 163
12	Post-Gd T1 VIBE 1#	TFE	TRA	380 x 299	150	3	shortest 2.9	shortest 6
13	Post-Gd T1 VIBE 2#	TFE	TRA	380 x 299	150	3	shortest 2.9	shortest 6
	*optional							

#Post-Gd scans should be performed with fat saturation / water excitation.

Extremities

INDICATION	**PROTOCOL**
Soft tissue tumour arising from the extremities	Before contrast agent administration: sequences 1 to 5
	During contrast agent administration: sequence 6
	After contrast agent administration: sequence 7 and 8 with SPIR
If possible mark swelling or scar	

PREPARATION	
Coil	Posterior and anterior
Contrast agent	**Gadolinium (for instance, Gadovist 0.1 ml per kg body weight)**

	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	SURVEY	FFE	MST						
2	T1 TSE	TSE	TRA	200 x 200	29	4	0.7 x 0.86	shortest 16	400 / 650
3	T2 TSE DIXON or T2 SPAIR	TSE	TRA	200 x 200	29	4	0.8 x 0.95	80	3500 / 5500
4	T1	TSE	SAG/COR	300 x 300	31	3	0.95 x 0.95	15	540 / 650
5	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map	EPI	TRA	200 x 200	40	4	2.5 x 2.5	72	4000-5000
6	DCE (start < 20 sec after infusion for fast temporal resolution)	TFE	TRA	200 x 200	8	5	1.17 x 2.94	1.3	5.4
7	Post-Gd T1 TSE SPAIR#	TSE	SAG/COR	300 x 300	36	3	0.95 x 0.9	15	450 / 650
8	Post-Gd T1 TSE SPAIR#	TSE	TRA	200 x 200	29	4	0.85 x 0.9	20	400 / 650

#Post-Gd scans should be performed with fat saturation / water excitation.

GE 3 T rhabdomyosarcoma MR template

Head and neck

INDICATION	PROTOCOL
Soft tissue tumour in the head or neck If possible mark swelling or scar	Before contrast agent administration: sequences 1 to 6 DCE optional

PREPARATION	
Coil	Head / neck
Contrast agent	**Gadolinium** (for instance, Gadovist 0.1 ml per kg body weight)

	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	Localizer	FGRE	MST						
2	T1	FSE	COR	180 x 180	33	3.0	0.45 x 0.5	15	450 / 700
3	T1	FSE	TRA	180 x 180	35	3.0	0.6 x 0.66	shortest 15	450 / 750
4	T2	FSE	COR	180 x 180	33	3.0	0.5 x 0.5	80	2500 / 6000
5	T2 Fat suppression	FSE	TRA	330 x 330	64	3.0	0.8 x 0.8	96	3000 / 4500
6	DWI (B=0; 100; 500; 1.000 s/mm2) and ADC map	SE EPI	TRA	230 x 196	41	3.0	2.0 x 2.0	shortest 75	4000-5000
7	Post-Gd LAVA[#]	LAVA (FGRE)	TRA	190 x 190	320	0.9	0.5 x 0.8	shortest 3.2	shortest 6.6
8	Post-Gd T1 IDEAL[#]	FSE	TRA	200 x 200	35	3.0	0.6 x 0.78	14	450 / 650
9	Post-Gd T1 IDEAL[#]	FSE	COR	180 x 180	33	3.0	0.6 x 0.78	14	450 / 650

[#]Post-Gd scans should be performed with fat saturation / water excitation.

Chest and abdomen

1.5 T recommended, see 1.5T protocol.

Extremities

INDICATION	PROTOCOL
Soft tissue tumour in extremity If possible mark swelling or scar	Before contrast agent administration: sequences 1 to 4 During contrast agent administration: sequence 7 After contrast agent administration: sequence 8 and 9 with **SPIR**

PREPARATION	
Coil	Posterior and anterior
Contrast agents	**Gadolinium** (for instance, Gadovist 0.1 ml per kg body weight)

	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	Localizer	FGRE	MST						
2	T1	FSE	TRA	250 x 250	30	4.0	0.8 x 1.1	10	400 / 750
3	T2 IDEAL	IDEAL FSE	TRA	250 x 250	30	4.0	0.87 x 1.09	80	shortest 2236
4	T1	FSE	SAG/COR	200 x 200	40	3.0	0.8 x 0.9	10	500 / 700

5	DWI (B=0; 100; 500; 1.000 s/mm2) and ADC map	SE EPI	TRA	230 x 230	50	4.0	2.5 x 2.5	shortest 54	4000-5000
6	DCE LAVA	LAVA(FGRE)	TRA	300 x 150	8	5.0	1.17 x 2.54	1.5	shortest 6.1
7	Post-Gd T1 FS[#]	FSE	SAG/COR	200 x 200	40	3.0	0.8 x 0.9	10	500 / 700
8	Post-Gd T1 FS[#]	FSE	TRA	250 x 250	30	4.0	0.8 x 1.1	shortest 10	400 / 750

[#]Post-Gd scans should be performed with fat saturation / water excitation.

GE 1.5 T rhabdomyosarcoma MR template

Head and neck

INDICATION	PROTOCOL
Soft tissue tumour in the head or neck If possible mark swelling or scar	Before contrast agent administration: sequences 1 to 6 DCE optional
PREPARATION	
Coil	Head / neck
Contrast agent	**Gadolinium** (for instance, Gadovist 0.1 ml per kg body weight)

	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	Localizer	FGRE	MST						
2	T1	FSE	COR	180 x 180	33	3.0	0.6 x 0.74	14	400 / 650
3	T1	FSE	TRA	180 x 180	35	3.0	0.6 x 0.74	16	400 / 650
4	T2	FSE	COR	180 x 180	33	3.0	0.45 x 0.5	100	2500 / 3500
5	T2 FS	Propeller FSE	TRA	330 x 330	64	3.0	1.0 x 1.0	shortest 76	shortest 6063
6	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map	SE EPI	TRA	200 x 200	41	4.0	2.81 x 2.81	shortest 71	4000-5000
7	Post-Gd LAVA[#]	LAVA FGRE	TRA	190 x 190	320	1.0	0.8 x 0.9	shortest 4.5	shortest 9.6
8	Post-Gd T1 IDEAL[#]	IDEAL FSE	TRA	180 x 180	35	3.0	0.7 x 0.92	14	400 / 700
9	Post-Gd T1 IDEAL[#]	IDEAL FSE	COR	180 x 180	33	3.0	0.7 x 0.94	14	400 / 700

[#]Post-Gd scans should be performed with fat saturation / water excitation.

Chest and abdomen

INDICATION			PROTOCOL
Soft tissue tumour in chest or abdomen			Before contrast agent administration: sequence 1 to 11
			After contrast agent administration: repeat Sequence 3 and 4 (=sequence 12 and 13)
			Sequence 7 to 11 set around the mass
Urogenital or prostate tumour			Sequence 9 and 10 are mandatory (tT2 TSE and sT2 TSE)
LOCATION TUMOUR	CHEST	First visit	DO NOT ACQUIRE sequence 9 and 10
		Follow up	DO NOT ACQUIRE sequence 9, 10 and 11
	UPPER ABDOMEN	First visit	DO NOT ACQUIRE sequence 9 and 10
		Follow up	DO NOT ACQUIRE sequence 9, 10 and 11
	PELVIC	First visit	ALL SEQUENCES
		Follow up	SELECTION OF SEQUENCE 7, 8, 9 and 10. NOT 11
PREPARATION			

Coil	Posterior and anterior
Contrast	**Gadolinium** (for instance, Gadovist 0.1 ml per kg body weight)

WITH ANESTHESIA (SMALL CHILD)

	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	Localizer	FGRE	MST						
2	3D T2 CUBE RT	FSE	COR	400 x 353	139	1.15	1.15 x 1.15	90	shortest 455
3	LAVA	LAVA FGRE	TRA	380 x 331	87	3.0	1.25 x 1.24	shortest 2.9	shortest 6
4	LAVA	LAVA FGRE	TRA	380 x 331	87	3.0	1.25 x 1.24	shortest 2.9	shortest 6
5	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map 1	SE EPI	TRA	380 x 332	26	5.0	2.81 x 3.5	shortest 78	4000-5000
6	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map 2	SE EPI	TRA	380 x 332	26	5.0	2.81 x 3.5	shortest 78	4000-5000
7	T1	FSE	TRA	250 x 250	65	4.0	0.7 x 0.8	8	400 / 600
8	T2 propeller FS	Propeller FSE	TRA	300 x 300	50	4.0	1 x 1	100	2227
9	T2	FSE	SAG	250 x 201	39	4.0	0.65 x 0.92	100	shortest 4029
10	T2	FSE	TRA	250 x 250	65	4.0	0.75 x 0.95	100	shortest 6671
11	LAVA Flex	LAVA FGRE	TRA	300 x 246	25	5.0	1.67 x 2.09	TE1: 2.3/ TE2: 4.3	shortest 6
12	Post-Gd LAVA[#]	LAVA FGRE	TRA	380 x 331	87	3	1.25 x 1.24	shortest 2.9	shortest 6
13	Post-Gd LAVA[#]	LAVA FGRE	TRA	380 x 331	87	3.0	1.25 x 1.24	shortest 2.9	shortest 6

* optional

[#]Post-Gd scans should be performed with fat saturation / water excitation.

WITHOUT ANESTHESIA (LARGER CHILD)

	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	Localizer	FGRE	MST						
2	T2 propeller	Propeller FSE	COR	450 x 450	35	5.0	1 x 1	100	shortest 2457
3	LAVA	LAVA FGRE	TRA	380 x 299	150	3.0	1.25 x 1.25	shortest 2.9	shortest 6
4	LAVA	LAVA FGRE	TRA	380 x 299	150	3.0	1.25 x 1.25	shortest 2.9	shortest 6
5	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map 1	SE EPI	TRA	380 x 380	45	5.0	2.81 x 3.49	shortest 78	4000-5000
6	DWI (b=0; 100; 500; 1.000 s/mm2) and ADC map 2	SE EPI	TRA	380 x 380	45	5.0	2.81 x 3.49	shortest 78	4000-5000

7	T1	FSE	TRA	250 x 250	65	4.0	0.75 x 0.8	8	400 / 600
8	T2 Propeller FS	Propeller FSE	TRA	300 x 300	63	4.0	1 x 1	shortest 57	shortest 2304
9	T2	FSE	SAG	250 x 201	39	4.0	0.65 x 0.92	100	shortest 4029
10	T2	FSE	TRA	250 x 250	65	4.0	0.75 x 0.95	100	shortest 6671
11	LAVA Flex	Flex FGRE	TRA	300 x 246	25	5.0	1.67 x 2.09	TE1: 2.3/ TE2: 4.3	shortest 163
12	Post-Gd LAVA#	LAVA FGRE	TRA	380 x 299	150	3	1.25 x 1.25	shortest 2.9	shortest 6
13	Post-Gd LAVA#	LAVA FGRE	TRA	380 x 299	150	3.0	1.25 x 1.25	shortest 2.9	shortest 6

*optional
#Post-Gd scans should be performed with fat saturation / water excitation.

Extremities

INDICATION	**PROTOCOL**
Soft tissue tumour arising from the extremities If possible mark swelling or scar	Before contrast agent administration: sequences 1 to 4 During contrast agent administration: sequence 6 After contrast agent administration: sequence 7 and 8 with **SPIR**
PREPARATION	
Coil	Posterior and anterior
Contrast agent	**Gadolinium** (For instance, Gadovist 0.1 ml per kg body weight)

	Sequence	Technique	Orientation	FOV [mm]	Slices	Thickness [mm]	Voxelsize [mm]	TE [ms]	TR [ms]
1	Localizer	FGRE	MST						
2	T1	FSE	TRA	200 x 200	29	4.0	0.7 x 0.86	shortest 16	400 / 650
3	T2 IDEAL	IDEAL FSE	TRA	200 x 200	29	4.0	0.8 x 0.95	80	3500 / 5500
4	T1	FSE	SAG/COR	300 x 300	31	3.0	0.95 x 0.95	15	540 / 650
5	DWI (B=0; 100; 500; 1.000 S/MM2) and ADC map	SE EPI	TRA	200 x 200	40	4.0	2.5 x 2.5	72	4000-5000
6	DCE LAVA	LAVA FGRE	TRA	200 x 200	8	5.0	1.17 x 2.94	1.3	5.4
7	Post-Gd T1 FS#	FSE	SAG/COR	300 x 300	36	3.0	0.95 x 0.9	15	450 / 650
8	Post-Gd T1 FS#	FSE	TRA	200 x 200	29	4.0	0.85 x 0.9	20	400 / 650

#Post-Gd scans should be performed with fat saturation / water excitation.

APPENDIX 16. IRS GROUP DEFINITION [90]

IRS Group	Definition
I	Localized tumor, completely removed with pathologically clear margins and no regional lymph node involvement
II	Localized tumor, grossly removed with (a) microscopically involved margins, (b) involved, grossly resected regional lymph nodes, or (c) both
III	Localized tumor, with gross residual disease after grossly incomplete removal, or biopsy only
IV	Distant metastases present at diagnosis

APPENDIX 17. DEFINITIONS OF RESPONSE

Definitions of primary tumour response (either 1D or 3D)

	1D assessment (RECIST 1.1)	**3D volumetric assessment**
CR: Complete remission	100% decrease	100% decrease
PR: Partial remission	≥ 30%, but < 100% decrease	≥66%, but < 100% decrease
SD: Stable disease	Neither PR or PD	Neither PR or PD
PD: Progressive disease	≥ 20% increase	≥ 73% increase

Definitions of metastatic response

CR: Complete remission	Complete remission of all metastatic lesions
PR: Partial remission	A response not meeting the definition of CR
SD: Stable disease	No clinically significant change in size or number of metastatic lesions
PD: Progressive disease	Increase in size or number of metastatic lesions

Definitions of lymph node response

N: Normalised	No current nodal involvement by imaging
PI: Persisting involvement	Continued involvement of lymph nodes by imaging
P: Progression	Increase in number of lymph nodes involved or increase in size of involved lymph nodes
PA: Persisting abnormality of uncertain significance	Continuing abnormality of lymph nodes with no confirmed tumour involvement
N/A (not previously involved.	No prior lymph node involvement

APPENDIX 18. DEFINITION OF SITES

To define the site of origin may be difficult in some cases of RMS. A correct site assignation is of importance in the choice of treatment. The following definitions are given to facilitate the clinician in the appropriate site classification.

We acknowledge the permission given by the IRSG to modify and use their original document on site definitions,

ORBIT

1. Eyelid

This site is sometimes erroneously designated as “eye”. Although there may occasionally be a case arising from the conjunctiva of the eye, the globe itself is not a primary site. The eyelid is much less frequent than the orbit itself.

2. Orbit

This refers to the bony cavity, which contains the globe, nerve and vessels and the extra-ocular muscles.

Tumour in this site will only rarely invade the bony walls and extend into the adjacent sinuses. This is why this tumour which is clearly adjacent to the skull base and its meninges is not by its natural history appropriate to include in the parameningeal sites unless there is invasion of bone at the base of the skull.

PARAMENINGEAL

1. Middle ear

This refers to a primary that begins medial to the tympanic membrane. This tumour is often advanced at presentation and because of extension laterally may present with a mass in front of or under the ear suggesting a parotid origin. It may also extend through the tympanic membrane and appear to be arising in the ear canal. When there is doubt about the site of origin, the “middle ear” designation should be picked as it implies the more aggressive therapy required of parameningeal sites.

2. Nasal Cavity and Para nasal Sinuses

The three Para nasal sinuses are the maxillary sinuses, the ethmoid sinuses, and the sphenoid sinus. These surround the nasal cavity, and a primary in one will frequently extend to another. It can be difficult to determine the exact site of origin, but the choice is academic as the treatment is not affected. The site designation will have a bearing on the design of radiotherapy portals. Tumour arising in the maxillary or the ethmoid sinuses may invade the orbit. This is much more likely than a primary in the orbit invading one of the sinuses. When the distinction between orbit and Para nasal sinus is unclear, the site selected should be Para nasal sinus as it is the more likely primary site and requires appropriately more aggressive therapy. A primary arising in the sphenoid sinus (rare) may extend inferiorly to involve the nasopharynx.

3. Nasopharynx

This refers to the superior portion of the pharynx which is bounded anteriorly by the back of the nasal septum, superiorly by the sphenoid sinus, inferiorly by a level corresponding to the soft palate, and laterally and posteriorly by the pharyngeal walls.

4. Infratemporal Fossa/Pterygopalatinand Parapharyngeal Area

This refers to the tissues bounded laterally by the medial lobe of the parotid gland and medially by the pharynx. Large tumours in this region may extend through the parotid gland and present as a mass of

the lateral face, sometimes extending even to the cheek. Where there is doubt as to the primary, the parameningeal designation should be chosen as it confers appropriately more aggressive treatment. The superior boundary of this tissue volume is the base of skull just under the temporal lobe, hence the term “infratemporal”. The distinction between this and the “parapharyngeal” area is academic.

5. Orbital tumours with bone erosion

Tumours arising in the orbit but with intracranial extension or important bone erosion are included in the parameningeal group.

In addition the following are classified as parameningeal tumours:

- Tumours involving vessels or nerves with direct intracranial connection (Arteria carotis interna, vertebralis, N. opticus, trigeminus, facialis etc).
- All intracranial and intraspinal tumours (but tumours arising from the paraspinal muscles with intraspinal extension should be designated as paraspinal, see “Other site” definition)
- All tumours with cranial nerve paresis (excluding parotid tumours with facial nerve palsy)
- CSF Tumour cell positive patients

HEAD AND NECK

1. Scalp

This site includes primaries arising apparently in, or just below, the skin of all the tissues of the face and head that are not otherwise specified below. This usually means the scalp, external ear and pinna, the nose and the forehead, but not the eyelids or cheek.

2. Parotid

The parotid gland lies just in front of, and under, the ear and may surround both sides of the posterior aspect of the ascending ramus of the mandible. As noted above, large primaries in the infratemporal fossa may erode through the parotid. A true parotid primary should not, on radiographic studies, reveal a mass in the infratemporal fossa.

3. Oral Cavity

This includes the floor of the mouth, the buccal mucosa, the upper and lower gum, the hard palate, the oral tongue (that portion of the tongue anterior to the circumvallate papillae). A primary arising in the buccal mucosa can be impossible to distinguish from one arising in the cheek, but the distinction is academic. This would also include those lesions arising in or near the lips.

4. Larynx

This refers to primaries arising in the subglottic, glottic, or supraglottic tissues. Tumours of the aryepiglottic folds can be impossible to distinguish from the hypopharynx, but the distinction is academic.

5. Oropharynx

This includes tumours arising from the anterior tonsillar pillars, the soft palate, the base of the tongue, the tonsillar fossa, and oropharyngeal walls. Tumours arising in the parapharyngeal space may indent the oropharyngeal wall. In this circumstance, the primary should be considered parameningeal. If the mucosa of the oropharynx actually contains visible tumour as opposed to being bulged by it, the primary would be oropharynx. Primaries arising in the tongue base, soft palate, or tonsillar region may extend into the oral cavity. The oropharynx designation is preferred.

6. Cheek

This refers to the soft tissues of the face that surround the oral cavity. Tumours arising in the parotid may invade the cheek. As noted above, the distinction between this and the buccal mucosa is academic.

7. Hypopharynx

This refers to the pyriform sinus and may be difficult to distinguish from larynx although the designation is academic.

8. Thyroid and Parathyroid

Primaries arising in these two sites are exceedingly rare, if they exist at all, and should those structures be involved, it would more likely be from a primary arising in an adjacent structure such as the neck or, rarely, the trachea.

9. Neck

This refers to the soft tissues of the lateral neck between the mastoid tip and the clavicle. It does not include those medial structures such as hypopharynx and larynx noted above. Unfortunately this site overlaps with the designation “paraspinal” included under the site group “trunk”. Primaries arising in the neck can and frequently do behave as a paraspinal primary with direct invasion into the spinal extra dural space, especially if posteriorly placed.

GENITO-URINARY BLADDER AND PROSTATE

Note: Bladder-Prostate primary tumours are now regarded favourable site based on favourable outcome in RMS2005 where these were treated according to the High Risk regimen. Based on their favourable outcome the TMG decided these should not be subject to High Risk randomisations but ALL should receive 9xIVA chemotherapy. **This means ALL Bladder-Prostate primaries should receive 9 x IVA irrespective of receiving radiotherapy**.

1. Bladder

Our criteria for identifying the bladder as a primary site has included the appearance of tumour within the bladder cavity, which can be biopsied under cystoscopy or occasionally at laparotomy. We do not recognize as primary bladder tumours those that simply displace the bladder or distort its shape. The latter are ordinarily primary pelvic tumours, unless otherwise specified.

2. Prostate

It is important to differentiate true prostatic tumours from pelvic tumours.

3. Bladder/Prostate

In approximately 20% of males with bladder or prostatic tumours, the precise site cannot be determined even at autopsy. The histologic features are similar. Although it is desirable to have an indication of the “most probable” site from the institution, and one should try to get this, it may not be possible.

GENITO-URINARY NON BLADDER AND PROSTATE

1. Paratesticular

The tumours arises from mesenchymal elements of the spermatic cord, epididymis, and testicular envelopes, producing a painless scrotal mass.

2. Testis

This designation is wrong because the tumours arise from paratesticular structures and may invade the testis.

3. Uterus

A tumour in this primary site may be difficult to differentiate from a primary vaginal site, because a tumour originating in the uterus (corpus or cervix) may fill the vagina. After a therapeutic response, the distinction is usually clear. In general there is a wide separation of age range between these two groups, with the vaginal cases occurring in infancy or early childhood and uterine primaries in adolescents or young adults.

4. Vagina

A patient with a primary vaginal lesion must have evidence of a visible tumour on the vaginal surfaces which can be biopsied through the vagina. Displacement or distortion of the vagina is not sufficient.

5. Vulva

Primary lesions in this site arise in the labia minora or majora.

EXTREMITIES

1. Hand

Refers to the area from the top of the fingers to the wrist

2. Forearm

Refers to the area from the wrist to the elbow joint

3. Arm

Refers to the area from the elbow joint to the shoulder joint. Tumours arising in the axilla are considered as extremity lesions.

4. Shoulder

The posterior aspect of the shoulder, i.e., the scapular area, is an extremity site.

5. Foot

Refers to the area from the toes to the ankle

6. Leg

Refers to the area from the ankle to the knee

7. Thigh

Refers to the area from the knee to the hip joint

8. Buttocks

These are extremity lesions.

OTHER SITES

This term conventionally groups tumours originating from the sites not mentioned above. Prognosis is similar and usually not satisfying.

The following specific sites have been defined:

1. Thorax

Includes tumours arising in the following sites:

a) Thoracic wall: includes tumours arising from the thoracic muscles and the parietal pleura

b) Mediastinum: occasionally a primary rhabdomyosarcoma may arise form trachea, heart or nearby areas

c) Lung: includes tumours arising form the lung parenchyma, bronchus and visceral pleura

d) Breast

e) Diaphragm

2. Abdomen

a) Abdominal Wall (including Lumbar or lumbo-sacral wall)

This refers to the anterior abdominal wall from the inferior costal margins superiorly to the inguinal ligaments and symphysis pubis, inferiorly, and extends laterally between the costal margin and posterior iliac crests to the paraspinal region.

b) Liver

True liver rhabdomyosarcoma are less frequent than bile duct tumours.

c) Bile duct

Bile Duct is a specific site and can be recognised as such at surgery. This might also be called “choledochus” or “biliary tract”. There is probably no way one can distinguish an intrahepatic bile duct site from a primary liver site except by examining the excised specimen.

d) Pancreas

e) Bowel

f) Abdomen

The term abdominal refers to tumours arising in the intraperitoneal cavity, when a specific organ of origin such as liver, bile duct, pancreas or intestine cannot be determined.

g) Retroperitoneum

The term retroperitoneal is reserved for those posteriorly situated abdominal tumours in which there does not seem to be a more specific site. Tumours in a retroperitoneal site are in the posterior aspect of the abdominal and/or pelvis. The term “psoas” as a site is not very specific, as the muscle extends through the posterior lower abdomen, pelvis and into the leg.

3. Paraspinal

When tumours are described as adjacent to the vertebral column, arising from the paraspinal muscles. This designation is preferable to “abdominal wall” or “trunk” or “neck”. They often show an intraspinal component and this should be specified.

4. Pelvis

It is difficult to define the site of origin when there is a large tumour in the abdomen. The pelvis designation is reserved for lesions involving the lower part of the abdomen when no more specific site is appropriate.

5. Perianal

These sites are ordinarily “perirectal” or “perianal”. They are distinguished with difficulty from perineal and

vulval sites; but the latter distinction is important.

6. Perineum

This should include the site which appear between the anus and the scrotum in males and the labia in females. It extends anteriorly to the base of the scrotum in males and to the introitus in females. It must be distinguished from labial and perianal sites.

APPENDIX 19. REGIONAL LYMPH NODE DEFINITION

Region	Definition
Extremities	
Upper extremity	Axillary, brachial, epitrochlear, infraclavicular nodes
Lower extremity	Inguinal, femoral, popliteal nodes
Genitourinary (GU)	
Bladder – prostate	pelvic (hypogastric, obturator, iliac, perivesical, pelvic, sacral, and presacral lymph nodes) (note: para-aortic nodes are distant nodes)
Cervix	pelvic (hypogastric, obturator, iliac, perivesical, pelvic, sacral, and presacral lymph nodes) (note: para-aortic nodes are distant nodes)
Uterus	pelvic, retroperitoneal nodes at renal vessels or below
Paratesticular / gonadal	Ipsilateral pelvic, retroperitoneal nodes at renal vessels or below (inguinal if the scrotum is involved)
Vagina	retroperitoneal, pelvic nodes at or below common iliac vessels, inguinal nodes
Vulva	Inguinal nodes
Head and neck	
Head / neck	Ipsilateral cervical, jugular, pre-auricular, occipital, supraclavicular nodes for laterally placed tumours (excluding scalp); may have bilateral adenopathy with centrally placed tumours
Orbit/Eyelid/ Cheek/External ear/Temporal region	parotid, ipsilateral jugular, pre-auricular, cervical nodes
Trunk	
Intrathoracic	Internal mammary, mediastinal nodes
Retroperitoneum/pelvis	Pelvic, retroperitoneal nodes
Intra-abdominal	Sub diaphragmatic, intra-abdominal and iliac lymph nodes according to site
Abdominal wall	Inguinal, femoral nodes
Chest wall	Axillary, internal mammary, infraclavicular nodes
Other	
Biliary / liver	porta hepatis nodes
Perianal, perineal	inguinal, pelvic nodes; may be bilateral

APPENDIX 20. HYPERTENSION BY AGE AND GENDER

Age, y	BP Percentile	SBP, mm Hg							DBP, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

*The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.

APPENDIX 21. EMA RECOMMENDATIONS FOR TRIAL RELATED BLOOD LOSS

Weight (kg)	Total blood volume (mL)	1% blood volume (mL)*	3% total blood volume (mL)*
5	425	4	12
10	850	8	24
15	1275	12	36
20	1700	17	51
25	2125	21	63
30	2550	25	75
35	2975	29	87
40	3400	34	102
45	3825	38	114
50	4250	42	126
55	4675	46	138
60	5100	51	103
65	5525	55	165
70	5950	59	177
75	6375	63	186
80	6800	68	204

* Per individual, the trial-related blood loss (including any losses in the manoeuvre) should not exceed 3 % of the total blood volume during a period of four weeks and should not exceed 1 % at any single time.

Time-points for the biological studies have been aligned in order to minimise invasiveness and reduce the volume of dead space blood that is removed from the patient. Where possible, blood for haematology and biochemistry analysis should be taken at the same times as the assay sample points for the same reasons. Investigators must seek advice from the Sponsor if there is a concern regarding the volume of study related blood loss for a particular patient.