A randomised phase I/II study of

Intensity **M**odulated **A**rc **T**herapy

techniques in abdominal **neuroblastoma**

Version 3.0

Date: 15-May-2018

Chief Investigator:	Dr Mark Gaze
Sponsor:	University of Birmingham
Sponsor's protocol number:	RG_14-015
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Cancer Research UK Clinical Trials Unit @CRCTU

CANCER RESEARCH UK

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Table of contents

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Randomisation Service

Provided by the CRCTU at the University of Birmingham.
Randomisation should be performed via the RDE system https://www.cancertrials.bham.ac.uk/IMATlive or over the phone by the CRCTU on:

0121 414 2996

SAE Reporting

SAEs should be faxed to the IMAT-Neuroblastoma Trial Office, CRCTU, University of Birmingham on:

0121 414 9520 or 0121 414 3700

IMAT-Neuroblastoma Trial Office

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Signature page

IMAT-Neuroblastoma Trial Protocol v3.0_vd15-May-2018

This protocol has been approved by:

Name:	Dr Mark Gaze	**Trial Role:**	Chief Investigator
Signature:		**Date:**	15/MAY/2018

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

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

SA-01	15-Aug- 2017	2.0	Substantial	• Addition of RT and eRDC to abbreviations
				• Section 6 – definition of complete and partial resection added
				• Re worded section 7.3.2 Arm B to "Intended dose of 36Gy in 24 fractions over 5 weeks (1.5Gy per fraction, treating Monday to Friday). If necessary, the dose should be reduced to as high a dose as is safely achievable with respect to normal tissue dose constraints"
				• Re worded section 7.3.3. Dose objectives table; Vertebrae to read
				  • "Dose to vertebrae superior and inferior to the PTV not included in the treatment field should be kept to D95% < 10Gy."
				  • "For vertebrae adjacent to the PTV this may not be achievable, so to limit spinal growth asymmetry, the following objectives should be met"
				• Section 7.3.3 Dose objectives table; Heart to read "Mean < 15 Gy"
				• Section 7.4.1
				  • Addition of Diagnostic imaging (CT and /or MRI) post induction chemotherapy/pre surgery used for target volume in

				Dicom format • Change from Diagnostic imaging (MRI +/- CT) used for target volume delineation in DICOM format to Diagnostic imaging (MRI +/- CT) from time of diagnosis in DICOM format • Addition of outlining submission form • Request for detailed anonymised planning note • Updated contact details • Corrected minor typographical and formatting errors throughout • Addition of ISRCTN number • Replacement of randomisation contact • Addition of Outlining submission form in figure 2 • Removal or references to the RTTQA Guidelines, updated to become RT Guidelines. • Change from international conference on harmonisation Guidelines for Good Clinical Practice to Good clinical Practice • Rewording Section 7.2.2 to clarify position on intravenous contrast • Section 7.11 Patient follow up updated to read • "No specific investigations are mandated" • "If a patient is well with no symptoms or signs to suggest recurrence, it will be inferred that no relapse has occurred."

SA02				• 7.3.3 Clarification to wording of the vertebral dose objectives section • 7.11 Clarification over early follow up • 8.1.15 Clarification over how to record acute toxicity • 8.2.1.4 Addition of list of expected events for this trial • 12.3 Clarification of Analysis of outcome measures • Updated contact details

Trial Synopsis

Title

IMAT-Neuroblastoma: A randomised phase I/II study of intensity modulated arc therapy techniques in abdominal neuroblastoma

Trial Design

An open, randomised, multicentre, UK trial to determine what dose of radiotherapy, higher than the standard dose of 21 Gray (Gy) and up to a maximum of 36Gy, it is feasible and safe to deliver using intensity modulated arc therapy (if judged better than conventional radiotherapy), in patients with high-risk neuroblastoma.

Objectives

Primary Objective

- To determine the radiotherapy dose, possibly higher than is currently standard and feasible, delivered by either IMAT or conventional radiotherapy techniques, for use in a subsequent international randomised phase III study

Secondary Objectives

- To estimate the acute and long term toxicities of radiotherapy for neuroblastoma delivered at two different intended dose levels
- To estimate the local control probability and survival in neuroblastoma when radiotherapy is delivered at two different intended dose levels
- The actual dose it is possible for 80% of patients to receive
- The proportion of patients in whom it is possible to deliver the randomly allocated dose using IMAT or (if better) conventional radiotherapy

Outcome Measures

Primary Outcome Measures

- The actual dose delivered to patients

Secondary Outcome Measures

- Acute toxicity
- Local control at two years after randomisation
- Long term side effects at five years after randomisation
- Event-free survival (EFS) and overall survival (OS)

Patient Population

Patients aged ≥ 18 months with high-risk neuroblastoma requiring radical radiotherapy

Sample Size

50 patients

Main Inclusion and Exclusion Criteria

Inclusion

- Any patient with high-risk neuroblastoma of the abdominal or pelvic regions who require radical radiotherapy
- Fit to receive radical radiotherapy
- Aged ≥ 18 months at diagnosis
- Informed consent from patient, parent or guardian
- Documented negative pregnancy test for female patients of child bearing potential
- Patient agrees to use effective contraception during treatment period (female patients of child bearing age only)

Exclusion

- Pregnant patient

Trial Duration

Recruitment period: 24 months. Patients will receive treatment over 3 or up to 5 weeks and will be followed-up for a minimum of 5 years.

Trial Office Contact Details

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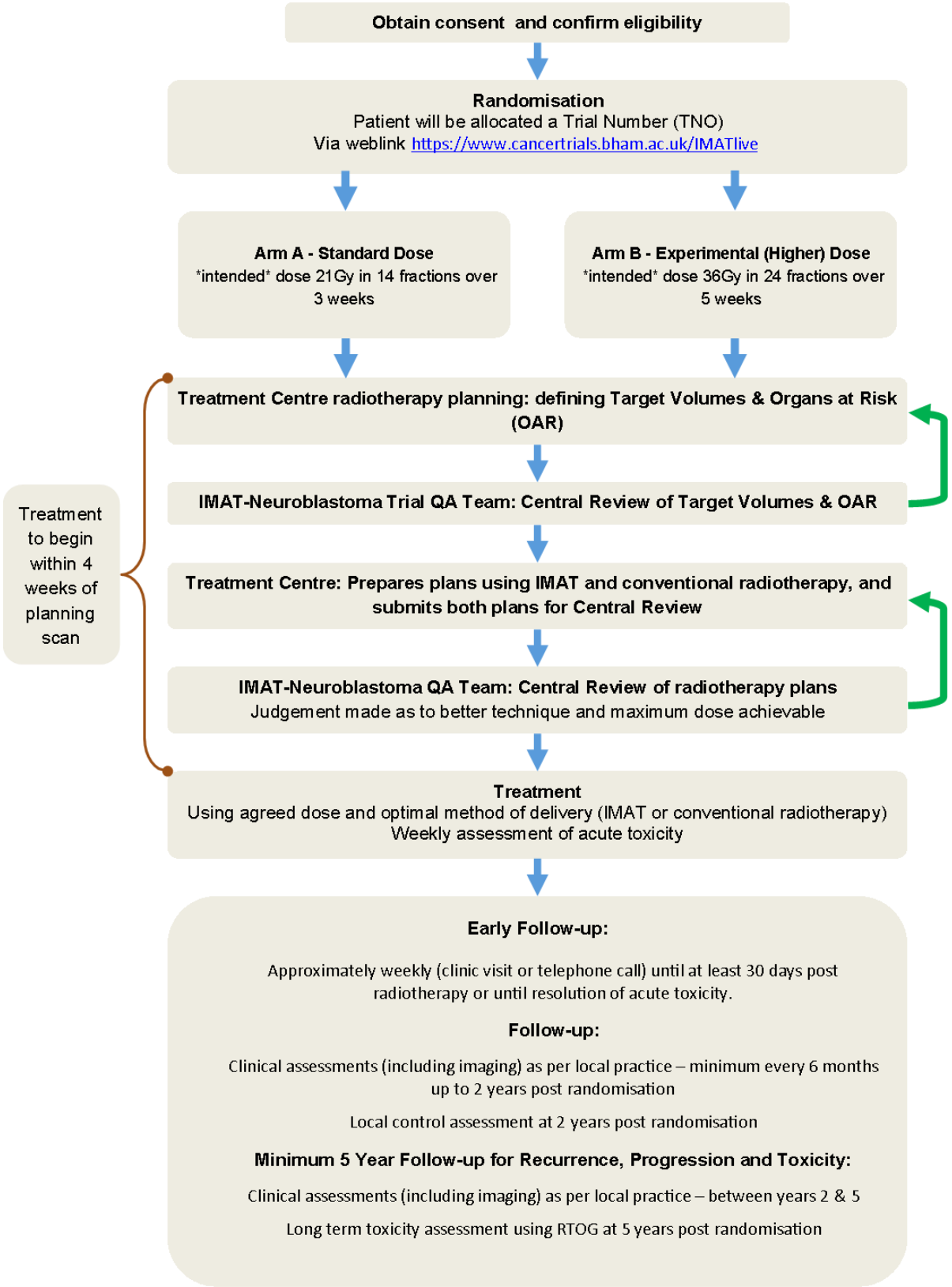
Trial Schema



Schedule of Events Table

Table 1 - Schedule of events flowchart

Activity	Screening	Randomisation	Pre-radiotherapy	During radiotherapy	EOT to EOT+30 days	Follow-up
Obtain consent	x					
Confirm Eligibility	x					
MYCN status results[1]		x				
INRG staging results[1]		x				
Operation note[1]		x				
Renal function assessment[2]			x			
Results from pre surgical cross sectional imaging[2]			x			
Planning CT scan[3]			x			
Radiotherapy outlining: define treatment volume and OAR at Treatment Centre[4]			x			
Central review of treatment volume and OAR[4]			x			
Preparation and review of radiotherapy plans at Treatment Centre[4]			x			
Central Review of radiotherapy plans[4]			x			
Radiotherapy delivery[5]				x		
Appointments during radiotherapy[6]				weekly		
Follow up appointments[7]					x	x
Adverse Event Reporting[8]				x	x	
Late toxicity reporting[9]						x
Local Control assessment[10]						x

1	In order to randomise a patient, information on MYCN status, INRG stage and a decision on the completeness of surgery is required. The results need to be to hand but the tests will have been performed as part of standard care pre-trial.
2	As part of patient preparation for radiotherapy planning the Treatment Centre requires the results of the following investigations: cross sectional imaging (MRI +/- CT) from diagnosis and before surgery (post induction chemotherapy), operation note, histopathology results from surgery and renal function assessment according to standard local practice. These would be required as part of standard preparation for radiotherapy planning.
3	Planning CT scanning to be performed as per section 7.2.2 of the protocol.
4	See sections 7.2, 7.3 and 7.4 of the protocol
5	See section 7 of the protocol
6	Patients will be reviewed weekly whilst having radiotherapy to assess for acute toxicity.
7	After completing trial treatment patients will have follow up appointments to check for acute toxicity (telephone consultation or clinic visit) at least weekly up to 30 days after last trial treatment was given or until resolution of the acute toxicity. Thereafter, follow-up according to established local protocols for clinical assessments and imaging (minimum every 6 months up to 2 years and then frequency as per local practice up to 5 years).
8	Adverse Events to be reported using CTCAE Version 4 from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.
9	Late toxicity will be recorded at 5 years after the patient was randomised according to the Late Toxicity RTOG scoring system – (see Appendix 4 - RTOG Late Toxicity). This information will be collected during routine clinic visits; no trial specific visits are required.
10	Patients should be reassessed for local control at 2 years after randomisation, unless relapsed. Assessment should normally be as per standard practice, mIBG scans and cross-sectional imaging are typically performed. In the absence of any other imaging modality being indicated for other purposes, ultrasound examination or MRI scan is preferred to avoid additional radiation exposure.

Abbreviations

ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
CBCT	cone beam CT
CRCTU	Cancer Research UK Clinical Trials Unit
CRF	Case Report Form
COG	Children's Oncology Group
CT	Computed Tomography
CTV	Clinical Target Volume
CV	Curriculum Vitae
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
DVH	Dose Volume Histogram
EFS	Event-free Survival
EOT	End of Treatment
eRDC	Electronic Remote Data Capture
GP	General Practitioner
GCP	Good Clinical Practice
GTV	Gross Tumour Volume
GTVp	Primary Gross Tumour Volume
GTVn	Nodal Gross Tumour Volume
Gy	Gray
ICF	Informed Consent Form
GCP	Guidelines for Good Clinical Practice
ICRU	International Committee of Radiation Units & measurements
ITV	Internal Target Volume
IMAT	Intensity Modulated Arc Therapy
IMRT	Intensity Modulated Radiotherapy
INRGSS	International Neuroblastoma Risk Group Staging System

ISF	Investigator Site File
kVCT	kilo voltage computerised tomography
LC	Local Control
MLC	Multi-Leaf Collimators
MRI	Magnetic Resonance Imaging
MYCN	N-myc proto-oncogene protein
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHS	National Health Service
NRES	National Research Ethics Service
OAR	Organs-At-Risk
OS	Overall Survival
PDD	Percentage Depth Dose
PTV	Planning Target Volume
QA	Quality Assurance
RCR	Royal College of Radiologists
R&D	Research and Development
REC	Research Ethics Committee
RR	Risk Ratio
RT	Radiotherapy
RTTQA	Radiotherapy Trials Quality Assurance
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SIOPEN	International Society of Paediatric Oncology Europe Neuroblastoma
TMG	Trial Management Group
TNO	Trial Number
UK	United Kingdom
WHO	World Health Organisation

1. Background and Rationale

1.1 Background

Neuroblastoma is the commonest solid tumour of childhood with an incidence of approximately 100 patients per year in the UK. The majority of cases are high risk disease, and the survival of these patients is approximately 40% or below at five years. Radiotherapy to the primary tumour site is standard practice following chemotherapy and surgery. It improves local control (LC) and may improve survival. However, the radiation tolerance of adjacent critical normal structures such as the kidneys and liver limit the dose of radiotherapy which can be delivered. This depends on the size and precise location of the neuroblastoma. Up to 50% of patients currently receive less than adequate radiotherapy doses. A new way of delivering radiotherapy - Intensity Modulated Arc Radiotherapy (IMAT) - offers a potential way to overcome some of the limitations through much better shaping of the volume treated to a high dose, and better avoidance of Organs at Risk (OAR) of damage. Gains et al have demonstrated, in a theoretical study, the ability of IMAT to deliver the standard radiotherapy dose to the tumour, avoiding normal structures, with greater reliability than conventional radiotherapy.

The aim of this feasibility study is to assess if, and to what extent, dose escalation is safely possible using IMAT in children with neuroblastoma; defining what increased dose might be suitable for use in future Phase III randomised studies. Acute and late toxicities will be monitored.

1.2 Trial Rationale

1.2.1 Justification for patient population

Neuroblastoma is a cancer of childhood arising from the cells of the sympathetic nervous system [1]. It is risk-stratified according to age, stage and molecular pathology [2, 3]. Unfortunately, survival in children with high-risk disease remains under 40% despite advances in multi-modality treatment [4, 5]. The mortality from neuroblastoma is disproportionately high compared with its incidence. Neuroblastoma accounts for 7% of malignant disease in childhood, but 15% of childhood cancer mortality.

Radiotherapy to the typically retroperitoneal primary tumour bed reduces the risk of local recurrence [6, 7] and this may impact on overall survival [8]. Radiotherapy is also indicated in selected patients with intermediate risk disease (although only high-risk patients will be recruited into this trial). It is hoped that completely novel treatments for neuroblastoma will improve survival, but so may improvements in the delivery of existing treatments, including radiotherapy.

Gains et al have, in a theoretical radiotherapy dosimetric planning study on a retrospective cohort of 20 conventionally treated patients, demonstrated that IMAT could indeed enable (1) the reduction or avoidance of the protocol non-compliance (under-dosage of the target volume in order to spare adjacent critical organs such as the kidneys) observed in a proportion of patients, and (2) better dosimetry in regard of tumour and normal tissues in patients in whom protocol compliance with standard treatment had been possible [9].

It may be that dose escalation beyond the current standard radiotherapy dose of 21Gy for high-risk neuroblastoma would translate into better outcomes in terms of the local control rate and possibly survival. However, dose escalation is not practicable using standard radiotherapy techniques within the constraints of normal tissue tolerance. The use of IMAT might facilitate safe dose escalation, but before such innovative therapies are introduced into routine clinical

practice, it is essential that they are scientifically evaluated in clinical trials. The potential benefit, and indeed potential risks, of IMAT must therefore be assessed in neuroblastoma.

1.2.2 Choice of treatment

Primary neuroblastoma tumours are not uniform. They differ in size and location, especially in relation to adjacent critical normal structures including the kidneys and liver. Conventional radiotherapy techniques often struggle to, or fail to, deliver the doses recommended in treatment protocols, because of the need to respect the tolerance of normal organs which are often immediately adjacent to the target volume.

The current International Society of Paediatric Oncology (Europe) Neuroblastoma (SIOPEN) [www.siopen.org/] Group's high-risk neuroblastoma protocol [10] aims to deliver 21Gy in 14 fractions to the Planning Target Volume (PTV). Within Europe, current standard practice is to deliver this with conventional anterior and posterior parallel fields [11]. Gains et al have shown that delivery of the full dose to the PTV is frequently limited however, by the proximity of the kidneys and the liver [12]. A compromise on target volume coverage or reduction in dose, or both, could have an impact on local control. Gains et al audited 41 patients Gains et al have treated with conventional radiotherapy and found that 20 (49%) had required a modification in dose or volume because of the tolerance of organs at risk. Quality assurance review of radiotherapy in 100 patients in the SIOPEN high-risk study has shown only 48% compliance with the protocol recommendations [12].

In the last few years radiotherapy delivery technologies have advanced significantly with the development of intensity modulated radiation therapy (IMRT), and in particular dynamic rotational treatments or arc therapy – IMAT. IMAT equipment is supplied by a number of manufacturers under their own trade names including RapidArc™ (Varian), VMAT™ (Eleckta) and TomoTherapy™ (Accuray). These offer the scope for treating irregularly shaped target volumes homogeneously, with much greater sparing of adjacent non-target normal tissues from the high dose irradiated volume, although there is greater exposure of normal tissues to low dose irradiation.

The majority of UK paediatric radiotherapy centres have installed this type of equipment and are developing expertise in its use in adult cancer treatment. There has been a reluctance to implement IMRT or IMAT in clinical practice in the absence of trials because of concern over the possible increased risk of carcinogenesis as a result of the greater volume of healthy normal tissues exposed to low dose irradiation, although it is possible that the risk of second cancers in patients treated with IMRT or IMAT may be reduced because there is very much less non target normal tissue exposed to high radiation doses.

Gains et al have developed radiotherapy Quality Assurance methodology [12] for use in the SIOPEN high-risk neuroblastoma trial. Gains et al have shown [2] in an international sample of 100 patients that the protocol has not been followed in just over half the cases. Usually this was because current treatment methods require a compromise on dose delivered or volume treated to avoid late radiation toxicity on normal organs.

Gains et al have performed a dosimetric radiotherapy planning pilot study [9] on 20 patients previously treated for neuroblastoma with conventional radiotherapy. This showed that the use of an IMAT technique would have enabled significantly better compliance with the protocol dose in 10 non-compliant cases, and a better dose distribution in 10 protocol compliant cases. A

future international Phase III randomised trial aims to answer the question "does a higher dose of radiotherapy lead to improved local control and/or survival in children with neuroblastoma". To do this, Gaze et al need to be able to identify a higher dose which can safely and consistently be used, given the fact that differences in the size and shape of the target volume mean that it is often difficult safely to administer the desired total dose. IMRT or IMAT should make this possible, and the present Phase I/II trial should demonstrate the best comparator dose to use in the future Phase III trial.

1.2.3 Justification for design

Recently developed sophisticated radiotherapy techniques such IMAT offer the possibility of improved radiotherapy dose distributions in many clinical situations. They allow better shaping of the high dose volume to irregularly shaped target volumes, and thus less high dose irradiation of healthy normal tissues in adjacent organs which if critical may be dose limiting. This improved therapeutic ratio comes at the cost of a greater exposure of normal tissues to low dose irradiation.

There will be a two way randomisation between two intended dose/fractionation schedules: the standard radiotherapy dose fractionation schedule (21Gy in 14 fractions); and a higher dose schedule (up to a maximum of 36Gy in 24 fractions). In both cases, the actual dose will be constrained by normal tissue tolerance, and so the dose delivered may be less than intended to ensure patient safety. Arm A is the standard dose arm (21Gy) and Arm B is the experimental arm (up to 36Gy).

The rationale for choosing 36Gy is:

1. It is, if deliverable, a significant increase (70%) over the standard dose of 21Gy. Therefore, if a clinical dose response relationship exists for this disease, a subsequent Phase III randomised study should demonstrate this.
2. 36Gy was the dose level used in two of a series of 20 neuroblastoma patients treated with IMRT, the mode dose was 23.4Gy [13]
3. 36Gy was the dose level used in a retrospective series of German patients where radiotherapy for residual disease was compared with unirradiated patients [14]
4. 36Gy is the dose used in some Children's Oncology Group (COG) protocols [15]

The prescribed doses in each arm are intended doses. Before the start of treatment, dosimetry will be performed for all patients (as is normal practice in radiotherapy) in relation to both the tumour PTV and also OAR principally kidneys and liver. The planning process (with central review) will ensure that, through the application of OAR dose constraints, the recognised tolerances of normal tissues will not be exceeded. It is recognised that this may mean in some cases that the full intended dose to the PTV is not safely deliverable, and a compromise lower dose has to be used.

Our expectation, based on our published pilot study [9] is that 21Gy should be deliverable with IMAT in almost all patients; whereas the safe delivery of 36Gy may be impossible in some patients, and a lower compromise dose will therefore be used. At the end of the study, Gaze et al will be able to identify the actual dose which can be given safely in 80% of patients.

The most serious complications of radiotherapy are usually late (and irreversible) side effects; acute side effects, although possibly unpleasant, usually subside in time. This study is therefore not like a conventional Phase I drug study where say three patients are treated at a certain dose level, and if no complications are manifest within a few weeks more groups of patients are treated at incrementally higher dose levels until unacceptable toxicities are seen. This study is randomised from the start, and patients are protected from avoidable harm by careful dosimetry in advance of treatment and regular review of toxicity data by the Data Monitoring Committee (DMC).

2. Aims, Objectives and Outcome Measures

2.1 Aims and Objectives

2.1.1 Primary Objective

- To determine the radiotherapy dose, possibly higher than is currently standard and feasible, delivered by either IMAT or conventional radiotherapy techniques, for use in a subsequent international randomised phase III study

2.1.2 Secondary Objectives

- To estimate the acute and long term toxicities of radiotherapy for neuroblastoma delivered at two different intended dose levels
- To estimate the local control probability and survival in neuroblastoma when radiotherapy is delivered at two different intended dose levels
- To determine the actual dose it is possible for 80% of patients to receive
- To determine the proportion of patients in whom it is possible to deliver the randomly allocated dose using IMAT or (if better) conventional radiotherapy

2.2 Outcome Measures

2.2.1 Primary Outcome Measures

- The actual dose delivered to patients in each treatment arm

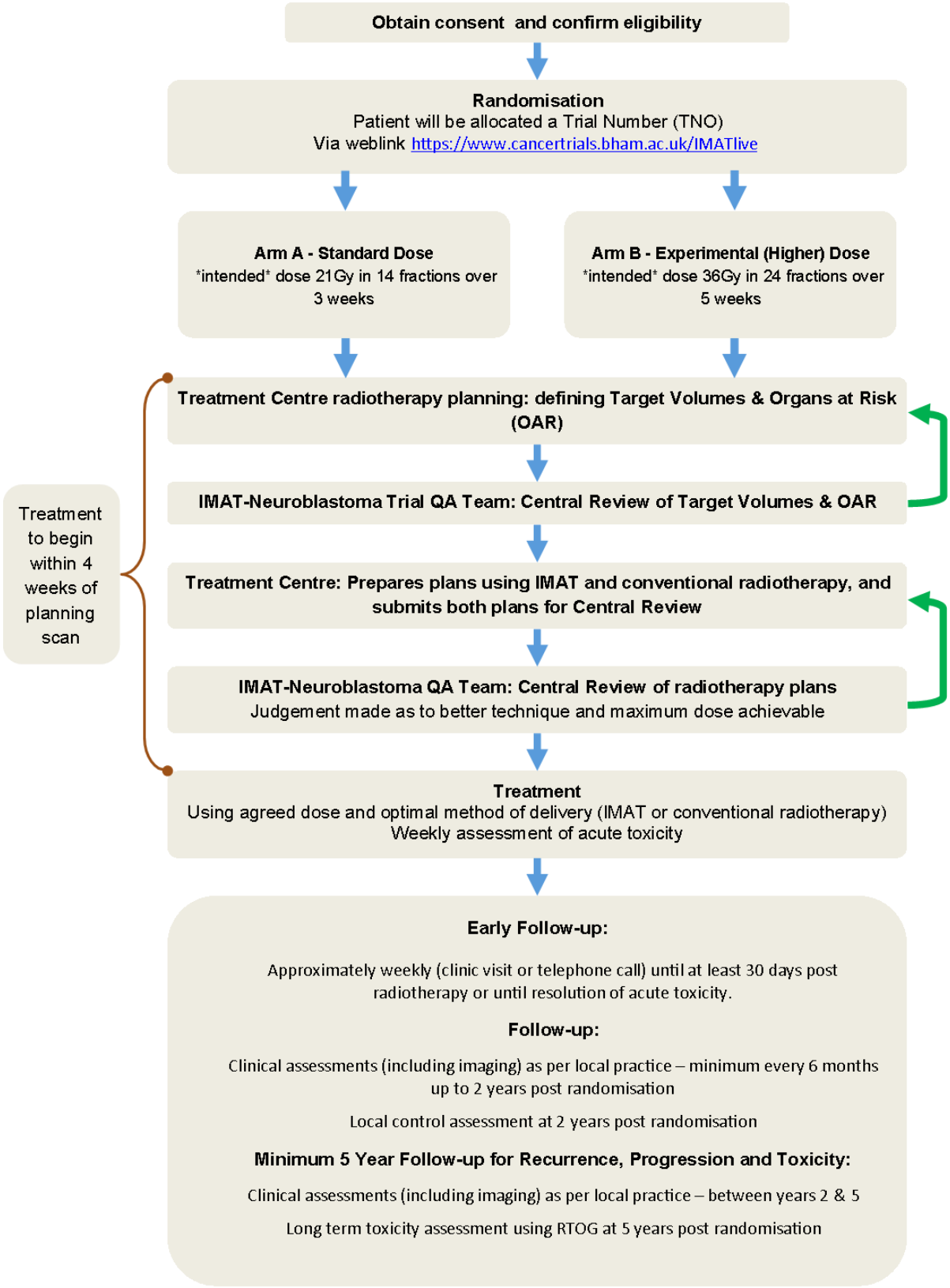
2.2.2 Secondary Outcome Measures

- Acute toxicity
- Local control at two years after randomisation
- Long term side effects at five years after randomisation
- Event-free (EFS) and overall survival (OS)

3. Trial Design

An open, randomised, multicentre, UK trial comparing the feasibility of safely delivering two intended radiotherapy doses: 21Gy (Arm A) and 36Gy (Arm B) in patients with high risk neuroblastoma.

Figure 1 - Overview of trial design



4. Eligibility

4.1 Inclusion Criteria

- Any patient with high-risk neuroblastoma of the abdominal or pelvic regions who require radical radiotherapy
- Fit to receive radical radiotherapy
- Aged ≥ 18 months at diagnosis
- Informed consent from patient, parent or guardian
- Documented negative pregnancy test for female patients of child bearing potential.
- Patient agrees to use effective contraception during treatment period (female patients of child bearing age).

4.2 Exclusion Criteria

- Pregnant patient

5. Screening and Consent

5.1 Screening

Investigators will be expected to maintain a Screening Log of all potential study participants. This Log will include limited information about the potential candidate (e.g. date of birth and sex), the date and outcome of the screening process (e.g. enrolled into study, reason for ineligibility, or refused to participate).

For patients who appear to meet the criteria for participation in the study, the Investigator will provide information to allow them/their parents to make an informed decision regarding their participation. If informed consent is given (see section 5.2), the Investigator will conduct a screening evaluation to ensure that the patient satisfies all inclusion and exclusion criteria. A patient /parent who gives written informed consent and whom the patient satisfies all the inclusion and exclusion criteria may be randomised into the study. Note that assessments conducted as standard of care do not require informed consent and may be provided as screening data. Assessments required in screening are listed in the schedule of events table.

5.2 Informed Consent

It is the responsibility of the Investigator (or delegate as stated on the Signature and Delegation log) to obtain written informed consent for each patient prior to performing any trial related procedure. A Patient/Parent Information Sheet is provided to facilitate this process.

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

If the patient/parent expresses an interest in participating in the trial they should be asked to sign and date the latest version of the Informed Consent Form (ICF). The Investigator or designate must then sign and date the form. A copy of the Informed Consent Form should be given to the patient, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once the patient is entered into the trial the patient's trial number (TNO) should be entered on the Informed Consent Form maintained in the ISF. In addition, a copy of the signed Informed Consent Form must be sent in the post to the Trial Office for review.

The trial includes both children and adults and written consent will be obtained from the patient whenever it is possible to do so and in accordance with the principles of consent where the underlying principle is not dependent on age but on that a child / young person's right to give consent is dependent upon their capacity to understand the specific circumstances and details of the research being proposed. Age appropriate Information Sheets are also available and there is a section on the Parent informed Consent Form where patients can document their assent if they wish to do so. For children who are not able to read, write or understand assent, the clinician will explain the trial in an age appropriate manner and if verbal assent is given by the child it will be documented in the patient's medical records.

Where a patient, who hasn't previously provided their own consent, reaches the age of 16 years of age during the trial (either whilst still on treatment or during follow-up) the Investigator should discuss the patient's wish to continue in the trial and obtain written informed consent at the earliest opportunity.

Details of the informed consent discussions should be recorded in the patient's medical notes, 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 Patient/Parent Information Sheet and Informed Consent Form. Throughout the trial the patient/parent 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/parent in which case the process above should be followed and the patient's right to withdraw from the trial respected.

Electronic copies of the Information Sheets and Informed Consent Form are available from the Trial Office and should be printed or photocopied onto the headed paper of the local institution.

With the patient's prior consent their General Practitioner (GP) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose.

6. Trial Entry

Patients can be entered into the trial once the Trial Office has confirmed that all regulatory requirements have been met by the trial centre and the site has been activated for randomisation. Informed consent from the patient/parent must be obtained and the eligibility criteria met by the patient prior to performing the randomisation. Randomisation should be performed by sites using the online remote data capture (eRDC) system. In order to randomise a patient, an eligibility

checklist must be completed. All of the required information – e.g. stratification factors – must be available at the time of randomisation.

Randomisation of patients can be achieved by logging on to the IMAT-Neuroblastoma eRDC system: **https://www.cancertrials.bham.ac.uk/IMATlive**

The program will allocate treatment via a computerised minimisation algorithm, developed by the Trial Office. Patients will be allocated in a 1:1 ratio.

Patients will be stratified by

- N-myc proto-oncogene protein (MYCN) amplification (yes, no, not known)
- Stage L2, M - as per (International Neuroblastoma Risk Group Staging System (INRGSS))
- completeness of surgery (complete resection, partial resection, no resection)

to ensure that there is a balance between treatments within the strata defined by these key prognostic factors.

For the purposes of this trial, 'complete' resection is defined as 90% or more. 'Partial' resection is defined as a substantial macroscopic amount of tumour remaining post- surgery as the surgeon was unable to remove 90% or more.

A copy of each randomisation result should be printed and retained in the ISF and the patient's hospital records.

7. Treatment Details

This section should be read in conjunction with the current version of the IMAT-Neuroblastoma Trial Radiotherapy planning, treatment delivery and QA guidelines (RT Guidelines).

7.1 Trial Treatment

Following randomisation, dosimetry will be performed for each patient in relation to both the tumour PTV and also OAR principally kidneys and liver. This will be performed locally as per standard practice.

The aim is to deliver the randomised intended dose to the PTV, recognising that the intended dose may be compromised by the need to respect tolerance doses of OAR.

Plans will be prepared locally by the Treatment Centre using both IMAT and conventional techniques, and treatment will be delivered according to which plan is judged (on the basis of standard IMAT parameters such as conformity index and homogeneity index, and review of Dose Volume Histograms (DVH) for OAR) following central review to have the best balance between target volume coverage to the randomised dose allocation, and sparing of OAR.

Other components of the multimodality therapy of neuroblastoma (chemotherapy, surgery, immunotherapy, etc.) and follow-up will be as per standard practice.

7.2 Outlining

7.2.1 Patient Preparation

- Cross sectional imaging using a Magnetic Resonance Imaging scan +/- a Computed Tomography Scan (MRI +/- CT) from diagnosis and before surgery (post induction chemotherapy)
- Operation note
- Histopathology from surgery
- Renal function assessment according to standard local practice

7.2.2 Image Acquisition

Patients should be scanned in the supine position.

Use of immobilisation devices is recommended (for example vac bag or wing board in place)

A treatment Planning CT with the patient in the treatment position is required. Centres should follow their local planning protocol; slice thickness ≤2.5mm would be expected.

Intravenous contrast should be used unless clinically contraindicated. Centres which do not routinely use intravenous contrast for radiotherapy planning scans in children may omit contrast if they are unable to change their standard practice.

General anaesthesia may be required for younger children.

Image acquisition should allow for whole kidneys, whole liver and at least 2 vertebrae above and below the superior and inferior extent of the PTV. If the volume may overlap any lung tissue, the whole thorax should be included in the scan to allow lung and heart DVH to be calculated. Typically the whole torso from the lung apices to the pelvic floor will be included.

7.2.3 Treatment Volumes outlining

7.2.3.1 Gross Tumour Volumes (GTV)

GTV is defined as the reconstructed tumour volume as seen on the post induction chemotherapy, pre-surgical imaging, or the gross residual tumour for inoperable cases, as well as any immediately adjacent persistently enlarged lymph nodes. This GTV will be trimmed where, following surgery, uninvolved normal organs such as liver, gut or kidney which were previously displaced have returned to their normal position. Information from the operation note and histopathology report should be used to ensure coverage of areas of potential residual disease which might not be apparent on imaging.

7.2.3.2 Clinical Target Volumes (CTV)

CTV is defined as the virtual GTV + 0.5cm. The margin should still be 0.5cm at points of contact with organs which were not infiltrated by tumour. It may be appropriate to include areas of microscopic spread as indicated from surgical note and histopathology report.

7.2.3.3 Internal Target Volume (ITV)

ITV is defined as the CTV taking into account Internal Motion of the tumour/ tumour bed and adjacent OARs.

7.2.3.4 Planning Target Volumes (PTV)

The CTV to PTV margin should be in accordance with departmental audit data, but typically PTV = CTV + 0.5cm. If necessary the PTV can be edited back from the 5mm patient external contour and renamed Plan PTV. Typically this will be 5mm but may differ across centres based on local audit evidence and anatomical site.

7.2.4 Organs At Risk

See the IMAT-Neuroblastoma RT guidelines for full details on OAR outlining.
The following structures will need to be outlined:

- Right and left kidneys
- Whole Liver
- Vertebrae
- Heart
- Lungs
- Gut
- Spinal canal

7.3 Planning

7.3.1 Planning Technique

Conventional radiotherapy technique

This will most frequently be an anterior and posterior parallel opposed field arrangement but there may be situations where a 3 field plan is required. Plans should be with the use of Multi Leaf Collimators (MLC), wedges and field weights as appropriate.

IMAT technique.

To be delivered with rotational arc therapies (Rapid Arc™, VMAT™ and Tomotherapy™).

7.3.2 Dose Prescription and Dose Fractionation

Dose Fractionation

- **Arm A** = 21Gy in 14 fractions over 3 weeks (1.5Gy per fraction, treating Monday to Friday)
- **Arm B =** Intended dose of 36Gy in 24 fractions over 5 weeks (1.5Gy per fraction, treating Monday to Friday). If necessary, the dose should be reduced to as high a dose as is safely achievable with respect to normal tissue dose constraints

- **Dose Prescription**
  - Conventional radiotherapy plans normalised with 100% prescription to a point in accordance with ICRU62
  - IMAT plans normalised with 100% prescription to the target volume median dose in accordance with ICRU83

Centres unable to prescribe to the median dose due to their planning system capabilities can alternatively prescribe to the mean dose and should record both the median and mean dose on the Plan Assessment Form and are expected to be within 0.5 Gy (up to 1Gy) of each other.

7.3.3 Treatment Volume and OAR Objectives

It is recognised that the dose objectives stated below are conservative and that slightly higher doses may be safe. The aim is to meet these objectives if possible, however if it is not possible, then higher doses may be accepted in the trial after discussion with the IMAT-Neuroblastoma Trial QA team (as part of the Central Review process).

Organ	Dose objectives
Kidneys	• For lateralised tumours where the ipsilateral kidney would receive the full / or near to full prescription dose, or where there is only one functioning kidney, the contralateral kidney V_{14} <10%, where V_{14} is the volume receiving 14Gy. • For midline tumours a combined V_{14} <40%
Liver	• V_{19Gy}<100% • V_{21Gy} <50%
Vertebra	• Dose to individual vertebrae superior and inferior to the PTV not included in the treatment field should be kept to **V10Gy < 5%**. • For vertebrae adjacent to the PTV this may not be achievable, so to limit spinal growth asymmetry, the following objectives should be met: Arm A 21Gy in 14#, vertebrae where **V10Gy < 5%** cannot be achieved should be irradiated to a V20Gy>95% Arm B up to 36Gy in 24#, vertebrae where **V10Gy < 5%** cannot be achieved should be irradiated to a V25Gy>95% Arm B patients where the achievable prescription dose is 25.5Gy in 17# or less, the adjacent vertebrae should meet the Arm A criterion of V20Gy>95%. This level of deviation from the intended Arm B dose is only expected for a limited number of challenging conventional plans. • Depending on patient geometry, e.g. the size of the intervertebral space, it may not be possible to meet the V10Gy < 5% criterion for the vertebrae immediately superior and inferior to the treatment field edge. The balance between dose to the adjacent vertebrae and these superior/inferior vertebrae is ultimately at the treating clinician's discretion, provided a rapid dose fall-off to less than 10Gy is produced in the superior-inferior direction.
Spinal canal	The maximum dose permitted to the spinal canal in this study is 30Gy. While the prescription dose of 36 Gy in 24# at 1.5Gy/# is within conventional spinal cord tolerance limits, a lower dose constraint has been mandated because of the risk of sensitisation of the spinal cord by high dose chemotherapy. Dose to 0.1cc of spinal canal ($D_{0.1cc}$) should be reported.
Lungs	V_{15Gy} < 10%

	V_{12Gy} < 25%
Heart	Mean < 15 Gy
GI Tract	V_{30Gy} < 10% V_{30Gy} < 50% V_{21Gy} <100%

See IMAT-Neuroblastoma RT guidelines for full details on PTV coverage and dose objectives.

7.4 Central Review

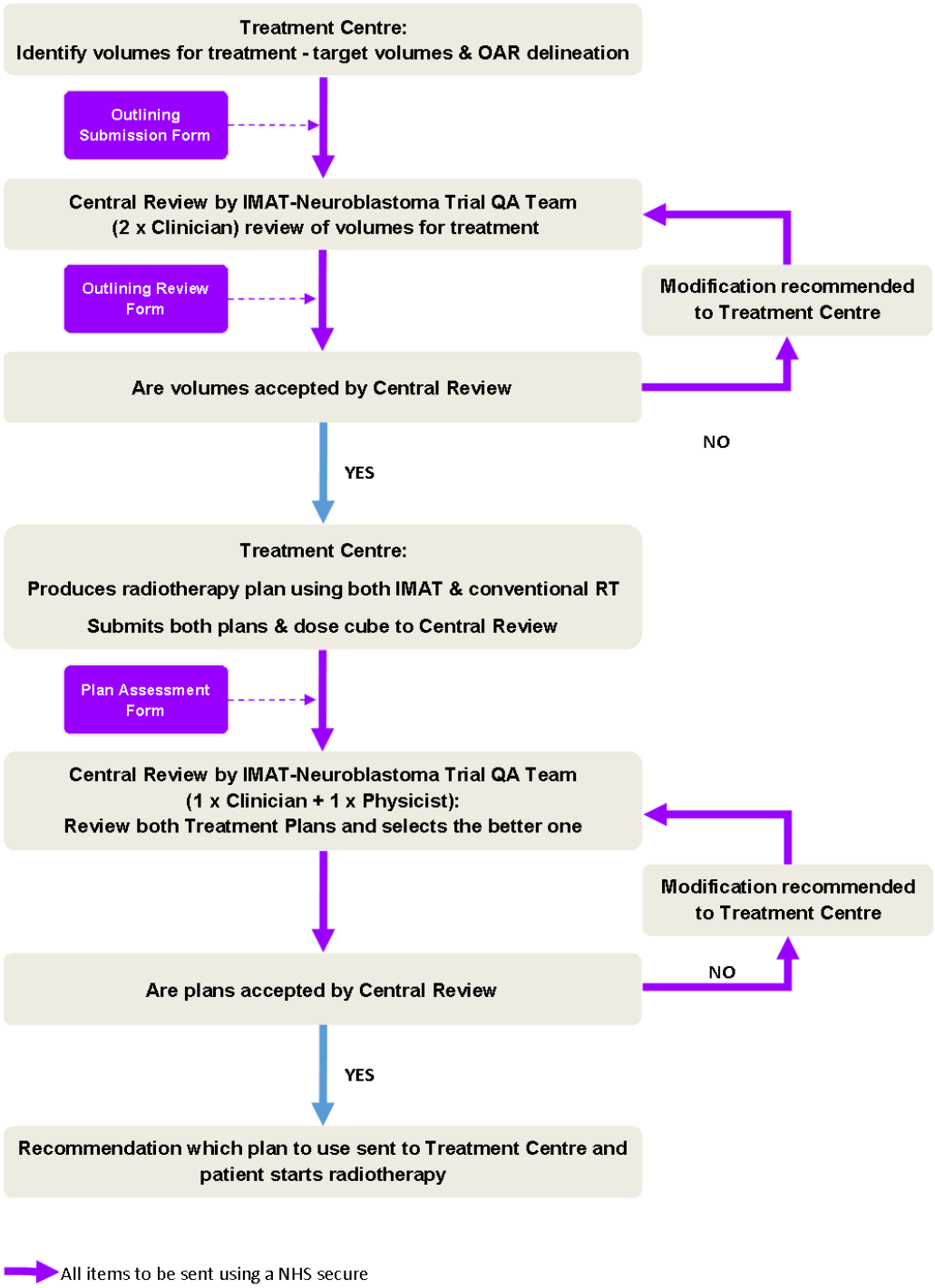
7.4.1 On-trial Central Review

There are 2 stages to the on-trial IMAT-Neuroblastoma Central Review process. Sites must obtain Central Review of both stages prospectively and sequentially for each individual patient.

- **Stage 1 (Outlining):**
  - Define areas for treatment – Target Volumes and OAR delineation
- **Stage 2 (Planning):**
  - Develop radiotherapy plans:
    - Using IMAT technique **AND**
    - Using conventional radiotherapy technique
    - Dose cube (dose summed for each plan)
  - Document these plans on the **Plan Assessment Form**

Central Review by the IMAT-Neuroblastoma Trial QA Team (on the basis of standard IMAT parameters such as conformity index and homogeneity index, and review of DVH for OAR) will either agree with Treatment Centre's proposals at each stage or suggest modifications and the Treatment Centre will need to resubmit an amended proposal for Central Review. Patients can only start treatment once an agreement has been reached between the IMAT-Neuroblastoma Trial QA Team and the Treatment Centre at Stage 2 of the Central Review process.

Figure 2 – Prospective Central Review Process



Data Collection for Prospective Central Review purposes

The following data should be submitted for **Stage 1** of prospective Central Review (target volumes and OAR delineation):

- Diagnostic imaging (MRI +/- CT) from time of diagnosis DICOM format
- Diagnostic imaging (CT and/or MRI) post induction chemotherapy/pre surgery used for target volume in DICOM format
- Planning CT images in DICOM format
- Structure sets in DICOM format, ensuring all CTVs, PTVs and OARs are present and correctly named using the trial nomenclature (as detailed in Appendix <3> of the RT Guidelines)
- In addition, it is very helpful to submit a detailed anonymised planning note to assist the reviewers in understanding which imaging data-sets, and their dates, have been used for delineation, and how non-imaging data (operation note and pathology report) may have been used to modify volumes.
- Outlining Submission Form

The following data should be submitted for **Stage 2** of prospective Central Review (planning)

- IMAT Plan in DICOM format
- Conventional radiotherapy plan in DICOM format
- Dose cube in DICOM format (dose summed for each plan, individual fields are not necessary)
- Plan Assessment Form

See the RT Guidelines Section E: Radiotherapy QA Process - sub section 3.2 for information on where to send and how to submit cases for prospective Central Review.

7.4.2 Retrospective Central Review

A retrospective central review will also be performed on the scans used to assess for Local Control.

7.5 Treatment Delivery and Verification

Treatment Centres should follow local guidelines as per departmental policy for on treatment imaging, and in line with Royal College Radiologists guidance [17] typically this will be:

- Conventional radiotherapy - KV OBI first 3 days then weekly
- IMRT - Daily KV OBI and weekly CBCT

Treatment should begin within 4 weeks of the planning scan being performed, if longer is required the patient must be discussed with the Chief Investigator (CI).

7.6 Radiotherapy Treatment Breaks and Compensation

Treatment breaks may result from severe acute toxicity or intercurrent illness, or machine breakdown. Interruptions for social reasons should be avoided. Any radiotherapy treatment break due to toxicity should be reported with documentation of reason in the Case Report Form (CRF). Any radiotherapy treatment break/prolongation of overall treatment time for causes other than acute toxicity or inter-current illness will be considered a protocol deviation and should be reported on the Deviation Form.

Patients in the IMAT-Neuroblastoma trial are managed as category 1 patients. Planned interruptions (machine servicing; bank holidays) should be managed by delivering fractions on other days of the week, and unplanned interruptions should be managed as per the Royal College of Radiologists guidelines [16]. If required, 2 fractions per day are permitted with a minimum inter-fraction interval of 6 hours.

7.7 Radiotherapy Trials Quality Assurance (RTTQA) Programme

The RTTQA programme for the trial will be co-ordinated by the National Radiotherapy Trials Quality Assurance group. Details on the QA programme and all required documentation can be found via the IMAT link at http://www.rttrialsqa.org.uk. The IMAT-Neuroblastoma RT Guidelines will be provided to Treatment Centres and should be adhered to for all IMAT-Neuroblastoma trial patients.

7.7.1 Pre-trial QA

Centres must successfully complete the Pre-trial QA programme in order to be activated for recruitment and approved to enter patients into the IMAT-Neuroblastoma trial. This process will be monitored by RTTQA. The full pre-trial QA process includes the following steps:

- Facility questionnaire (FQ)
- Benchmark cases (Outlining and Planning)
- Dosimetry audit

7.7.2 On-trial QA

On-trial QA in the form of prospective individual case central reviews will be performed by the IMAT-Neuroblastoma Trial QA Team for all patients in the trial. See section 7.4.1 for further details.

7.8 Assessments

7.8.1 Baseline Results required for Treatment Planning

As part of patient preparation for radiotherapy planning the Treatment Centre requires the results of the following investigations:

- Cross sectional imaging (MRI +/- CT) from diagnosis and before surgery (post induction chemotherapy)
- Operation note
- Histopathology results from surgery
- Renal function assessment according to standard local practice

7.8.2 Assessment of acute toxicity whilst receiving radiotherapy

Patients will be reviewed weekly by their Clinician whilst they are receiving radiotherapy to assess for any acute toxicity.

7.9 Supportive Treatment

Supportive treatment to be performed as per local policy and as required clinically.

7.10 Concomitant Medication

No chemotherapy, hormonal anticancer therapy or experimental anticancer medications other than those study-related will be permitted while the patient is receiving study treatment. In case of disease progression requiring other forms of specific anti-tumour therapy, investigators should give whatever therapy is considered appropriate.

7.11 Patient Follow-up

All patients, provided that they have not withdrawn consent to follow-up, should have long-term follow-up at 5 years after randomisation, irrespective of whether they discontinued study treatment prematurely. The anticipated frequency is:

Early Post Radiotherapy Follow-up:

- Follow-up appointments approximately weekly and documentation of acute toxicity from End of Treatment (EOT) for 30 days post radiotherapy . These follow up appointments may be done over the telephone and clinic visits only arranged if clinically necessary

Late Follow-up and Response Assessment:

- Thereafter, follow-up according to established local protocols for clinical assessments and imaging (minimum every 6 months up to 2 years post randomisation and then frequency as per local practice up to 5 years)
- Local control - patients should be reassessed at 2 years from randomisation unless relapsed. No specific investigations are mandated. Assessment should normally be as per standard practice. mIBG scans and cross-sectional imaging are typically performed. In the absence of any other imaging modality being indicated for other purposes, ultrasound examination or Magnetic Resonance Imaging (MRI) scan is preferred to avoid additional radiation exposure. If a patient is well with no symptoms or signs to suggest recurrence, it will be inferred that no relapse has occurred.

Late toxicity assessment will be recorded at 5 years post randomisation using the RTOG scoring systems. (See Appendix 4)

Information about a patient's survival outcome may be collected past 5 years, until all patients have a minimum of 5 years follow-up.

7.12 Treatment Discontinuation and Withdrawal of Consent

7.12.1 Treatment Discontinuation

Patients should discontinue trial treatment in the following circumstances:

- The patient/parent chooses to discontinue treatment and/or terminate participation in the trial
- The Investigator considers that continuation is not in the best interest of the patient
- Progressive disease according to clinical investigations or radiographic investigations

A Treatment Discontinuation Form should be completed to document the reason for treatment discontinuation. All participants who discontinue radiotherapy or withdraw from the trial follow up schedule due to adverse events (AEs) including clinical laboratory abnormalities must be followed up until they recover, until the event has stabilised, or until the event or laboratory

value returns to baseline level. The outcome (resolved or ongoing) of these AEs must be recorded in the CRF.

7.12.2 Patient Withdrawal

Patients and their parent/guardians are free to withdraw from the study at any time. In the event of a patient's/parent's decision to withdraw from the study, the Investigator should ascertain from which aspects of the study the patient wishes to withdraw (see below). The details of patient withdrawal (date and reasons for withdrawal) should be clearly documented in the source data. A Withdrawal of Consent Form should be completed and returned to the Trial Office.

- The patient would like to withdraw from trial treatment, but is willing to be followed up according with the schedule of assessments (i.e. the patient has agreed that data can be collected and used in the trial analysis)
- The patient would like to withdraw from trial treatment and does not wish to attend study visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits (i.e. the patient has agreed that data can be collected at standard clinic visits and used in the trial analysis
- The patient would like to withdraw from trial treatment and 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)

8. Adverse Event Reporting

The collection and reporting of Adverse Events (AEs) will be in accordance with the Research Governance Framework for Health and Social Care and the requirements of the National Research Ethics Service (NRES). Definitions of different types of AE are listed in Appendix 2. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the protocol.

8.1 Reporting Requirements

8.1.1 Adverse Events

All medical occurrences which meet the definition of an AE (see Appendix 2 for definition) should be reported. Please note this includes grade 3 and grade 4, CTCAE version 4, abnormal laboratory findings.

8.1.2 Serious Adverse Advents

Investigators should report AEs that meet the definition of an SAE (see Appendix 2 for definition)

8.1.3 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 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 Case Report Form

8.1.4 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 becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the Trial Office as soon as possible. Once consent has been obtained provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form. If appropriate also complete an SAE Form as detailed below.

8.1.5 Reporting Period

Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.

Within the CRF, if the toxicity resolves before the 30 days, the end date is recorded, otherwise the toxicity will be recorded as ongoing at 30 days.

8.2 Reporting Procedure

8.2.1 Site

8.2.1.1 Adverse Events

AEs experienced during treatment should be recorded in the toxicity section of the Treatment Acute Toxicity Form.

AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see Appendix 3). Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE 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.

Long term toxicity will be scored using the RTOG scoring system. This will be documented on CRFs from 30 days after last administered treatment and at 5 years post randomisation.

8.2.1.2 Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in the ISF.

AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 8.1 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 faxed together with a SAE Fax Cover Sheet to the Trial Office using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form with an SAE Fax Cover Sheet to:

0121 414 9520 or 0121 414 3700

On receipt the Trial Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the Trial Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the Trial Office 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 Trial Office in the post and a copy kept in the ISF.

Investigators should also report SAEs to their own Trust in accordance with local practice.

8.2.1.3 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).

8.2.2 Trial Office

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 reasonable causal relationship with the trial treatment will be regarded as a related SAE. The Clinical Coordinator will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

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

	Short Term Events	Long term Events	Either short or long term events
Vomiting	X		

Diarrhoea	X		
Constipation	X		
Erythema	X		
Epilation	X		
Anorexia	X		
Nausea	X		
Lymphocyte count decreased	X		
Neutrophil count decreased	X		
Platelet count decreased	X		
White blood cell count decreased	X		
Moist desquamation	X		
Fever	X		
Febrile neutropenia	X		
Infections	X		
Insufficiency fracture		X	
Radiation induced malignancy		X	
Bowel ulceration/ perforation/ stenosis		X	
Bowel changes		X	
Skeletal muscle/ Radiation fibrosis		X	
Difficulty swallowing			X
Shortness of breath/ breathing problems			X
Dry/ Sore Skin			X
Change of skin colour/ pigmentation/ depigmentation			X

Skin reaction (CTCAE term: Dermatitis Radiation)			X
Reduced bone marrow reserve			X

8.2.3 Reporting to the main Research Ethics Committee

8.2.3.1 Unexpected and Related Serious Adverse Events

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

8.2.3.2 Other safety issues identified during the course of the trial

The main REC will be notified immediately if a significant safety issue is identified during the course of the trial.

8.2.4 Investigators

Details of all Unexpected and Related SAEs 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.

8.2.5 Data Monitoring Committee (DMC)

The independent DMC will review all SAEs.

9. Data Handling and Record Keeping

9.1 Data Collection

This trial will use an eRDC system for completion of the CRF. Access to the eRDC system will be given to individuals via the IMAT-Neuroblastoma Trial Office. The IMAT-Neuroblastoma eRDC system can be accessed from:

https://www.cancertrials.bham.ac.uk/IMATlive

If the eRDC system is unavailable for an extended period of time a paper based CRF should be completed and forms returned to the IMAT-Neuroblastoma Trial Office for data entry.

Please Note: SAE reporting will be paper-based throughout the course of the trial (refer to section 8.2.1.2)

The CRF must be completed, signed/dated and returned to the Trial Office by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the timeframe listed above. The exception is the SAE Form which must be co-signed by the Investigator.

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 clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

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 completed originals should be sent to the Trial Office and a copy filed in the ISF.

Trial forms may be amended by the Trial Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, sites will be notified of new versions when they become available on the eRDC. New versions of the SAE form must be implemented by participating sites immediately on receipt. Acknowledgement of receipt should be sent to the IMAT-Neuroblastoma Trial Office.

9.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, 'patients' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 10 years after the end of the trial. Do not destroy any documents without prior approval from the CRCTU Document Storage Manager.

10. Quality Management

10.1 Site Set-up and Initiation

Sites will be set up and initiated by the IMAT-Neuroblastoma Trial Office. All sites will be required to sign a Clinical Study Site Agreement prior to participation. In addition, all participating Investigators will be asked to sign the necessary agreements and supply a current Curriculum Vitae (CV). All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the IMAT-Neuroblastoma Trial Office.

Prior to commencing recruitment, all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting which will cover aspects of the trial design, protocol procedures, AE reporting, QA, collection and reporting of data and record keeping.

Sites will be provided with an ISF containing essential documentation and instructions required for the conduct of the trial by the Sponsor. The IMAT-Neuroblastoma Trial Office must be informed immediately of any change in the site research team.

10.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the CRCTU Quality Management Plan (QMP). Additional on-site monitoring visits may be triggered for

example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required the Trial Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the IMAT-Neuroblastoma trial staff access to source documents as requested.

10.3 Central Monitoring

Where a patient has given explicit consent sites are requested to send in copies of signed Informed Consent Forms for in-house review.

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be sent Data Clarification Forms requesting 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 Trial Management Group or Data Monitoring Committee and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the main REC.

10.4 Audit and Inspection

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

10.5 Notification of Serious Breaches

The Sponsor of the trial is responsible for notifying the REC in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

Sites are therefore requested to notify the Trial Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trial Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

11. End of Trial Definition

The end of trial will be 6 months after the last data capture. The Trial Office will notify the main REC that the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial.

12. Statistical Considerations

12.1 Definition of Outcome Measures

12.1.1 Primary Outcome Measures

- The actual dose delivered to patients

12.1.2 Secondary Outcome Measures

- Acute toxicity - recorded using CTCAE v4
- Local control at two years after randomisation. Will be assessed as a time-to-event outcome (Time to local failure), Patients will be censored at death and it will be considered a competing risk. Local failure is defined as local recurrence on imaging in those patients in whom there was no gross residual disease at the time of treatment, or local progression of the residual mass in those patients who at the time of treatment had gross residual disease detectable on imaging.
- Long term side effects up to five years after randomisation - recorded using RTOG grading system.
- EFS and OS – EFS and OS will be measured from randomisation to the date of an 'event' or death respectively. Patients lost to follow-up will be censored accordingly at date last seen. An event is defined as progression, recurrence, death without progression/recurrence and secondary malignancies.

12.2 Sample size considerations

This is a feasibility study, so not designed to address the relative efficacy and toxicity of different doses.

It is planned to recruit 50 patients (about 25 in each arm) over a two year period, this figure was chosen due to recruitment availability and as it seemed a pragmatic number of patients to complete the primary objective of the trial. The trial is not designed to assess for a pre-specified difference in local control rate across treatment arms and thus is not powered to do so.

12.3 Analysis of Outcome Measures

The primary outcome will be analysed on both an intention-to-treat (ITT) population and a 'per-protocol' population which contains only those patients who received radiotherapy. All secondary time-to-event analyses will be based on the ITT principle. The secondary outcomes for toxicity will exclude patients who did not start their allocated treatment. As this is a feasibility study all analysis will be descriptive in nature.

The actual dose delivered to patients in each treatment arm will be summarised, using means (with Confidence Intervals) and median (with interquartile range).

Toxicity will be summarised and presented accordingly for each arm and overall. Acute toxicity will be recorded using CTCAE v4, whilst long term toxicity will be recorded using RTOG grading system.

The end point of two year local control will require follow-up for two years after the last patient has randomised and the first main analysis will be presented at this time point. Local control will be assessed through the use of Kaplan-Meier plots of a time-to-event outcome (Time to local failure). Hazard ratios (with confidence intervals) from Cox regression analysis will be reported for comparison of the two arms.

The absolute dose and the percentage of the full protocol dose (as assigned at randomisation) actually delivered will be recorded for each patient.
Acute toxicity will be evaluated according to National Cancer Institute (NCI) common toxicity criteria AE version 4. Frequency, grade and type of toxicity will be recorded.

EFS and OS will be assessed through the use of Kaplan-Meier plots. Hazard ratios (with confidence intervals) from Cox regression analysis will be reported for comparison of the two arms.

The randomisation and stratifications described are to minimise the risk of chance imbalances between the two arms. These stratification factors (MYCN status, INRGSS stage and completeness of surgery) have been utilised as they are key prognostic factors. The data required for the primary endpoint in each patient (actual dose administered) can be determined immediately after treatment of each patient, so the principal finding of this trial will be available very shortly after recruitment is complete. Acute toxicity can also be reported very soon after the final patients have completed treatment and been followed for a few weeks.

12.4 Planned Interim Analyses

Interim analyses will be submitted at regular intervals to the Independent DMC. The analysis will focus on summary statistics of actual dose and the acute toxicity profile of the treatment.

12.5 Planned Main Analyses

The first main analysis to determine the proportion of patients receiving full dose treatment with each technique, the possibility for dose escalation and a descriptive analysis of acute toxicity will be performed following completion of trial treatment.

The outcome of two year local control will require follow-up for two years after the last patient has been randomised. There will be some attrition related to metastatic relapse and death – this will be controlled for with analysis of local recurrence free probability at two years using Kaplan-Meyer plots, with patients censored at death. The full evaluation of the effect of dose escalation on local control probability and survival will require a subsequent randomised phase III trial.

Late effects can only be determined after a significant period of time has elapsed, by which time many patients will have died. It is estimated that about one third of patients (about eight in each arm) will be alive at 5 years for a late effects assessment. This is too small a number for quantitative conclusions to be drawn, but may highlight any major unexpected late effects.

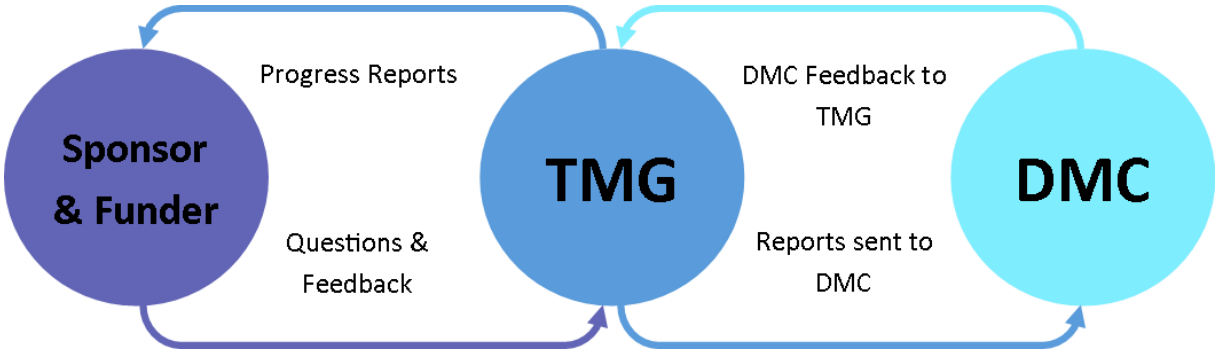
12.6 Stratification

Patients will be stratified by

- N-myc proto-oncogene protein (MYCN) amplification (yes, no, not known)
- Stage L2, M - as per International Neuroblastoma Risk Group Staging System (INRGSS)
- completeness of surgery (complete resection, partial resection, no resection)

to ensure that there is a balance between treatments within the strata defined by these key prognostic factors. There will be no formal subgroup analyses by these parameters.

13. Trial Organisational Structure



13.1 Sponsor

This trial is sponsored by the University of Birmingham.

13.2 Coordinating Centre

The trial is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham according to their local procedures.

13.3 Trial Management Group

The Chief Investigator, Co-investigators, Trial Statistician, Trial Manager, Senior Trial Coordinator, Trial Coordinator and Trial Monitor will form the TMG. The TMG will be responsible for the day-to-day conduct of the trial, meeting at regular intervals (e.g. every 3 months), or as required, usually by teleconference. They will be responsible for the set-up, promotion, on-going management of the trial, the interpretation of the results and preparation and presentation of relevant publications.

13.4 Data Monitoring Committee

Analyses will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will be scheduled to meet, prior to the trial opening, 6 months after the trial opens to recruitment and bi-annually thereafter. Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TMG. The TMG will consider the DMCs findings and make recommendations to the Sponsor and funder. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety.

14. Finance

This is an Investigator-initiated and Investigator-led trial funded by Cancer Research UK. No individual per patient payment will be made to NHS Trusts, Investigators or patients. This study has been adopted into the NIHR CRN Portfolio.

15. Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Data Protection Act 1998 and the Guidelines for GCP. The protocol will be submitted to and approved by the main REC prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local Research & Development (R&D) approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the Trial Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local 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.

16. 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 Data Protection Act 1998. With the patient's consent, their initials, date of birth, NHS number, or in Scotland the Community Health Index (CHI), will be collected at trial entry. Patients will be identified using only their unique TNO and initials on the Case Report Form and correspondence between the Trial Office and the participating site. However patients are asked to give permission for the Trial Office to be sent a copy of their signed Informed Consent Form 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 Trial Office (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 Trial Office will maintain the confidentiality of all patients' data and will not disclose information by which patients may be identified to any third party. Representatives of the IMAT-Neuroblastoma trial team may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

Non-anonymised copies of patients' scans required for treatment planning, review and quality assurance purposes will be transferred to the IMAT-Neuroblastoma Trial QA Team at University College London Hospital, using a secure NHS method. This is a standard NHS procedure used for transferring images between hospitals. Patients will consent for such transfer. This non-anonymised data will be kept confidential and patient data can only be accessed by authorised personnel.

17. Insurance and Indemnity

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

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The University of Birmingham cannot offer indemnity for non-negligent harm. 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.

18. 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.

Appendix 1 - WMA Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians
in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION
It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. 4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress.

In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

Appendix 2 - Definition of Adverse Events

Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the treatment received.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Related Event

An event which resulted from the administration of any of the research procedures.

Serious Adverse Event

An untoward occurrence that:

- Results in death
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of 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.

Unexpected and Related Event

An event which meets the definition of both an Unexpected Event and a Related Event.

Unexpected Event

The type of event that is not listed in the protocol as an expected occurrence.

Appendix 3 - Common Toxicity Criteria Grading's

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. 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

A copy of CTCAE v4.0 is contained within section 6 of the ISF

Appendix 4 - RTOG Late Toxicity

Instructions

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When two criteria are available for similar toxicities, the one resulting in the more severe grade should be used.
3. Toxicity grade = 5 if that toxicity caused the death of the patient.
4. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.
5. An accurate baseline prior to start of therapy is necessary.

Toxicity	0	1	2	3	4
SKIN	None	Slight atrophy Pigmentation change Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosia) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture <10% linear reduction	Severe induration and loss of subcutaneous tissue Field contracture >10% linear measurement	Necrosis
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia Little mucous	Marked atrophy with complete dryness Severe telangiectasia	Ulceration
SALIVARY GLANDS	None	Slight dryness of mouth Good response on stimulation	Moderate dryness of mouth Poor response on stimulation	Complete dryness of mouth No response on stimulation	Fibrosis
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadraplegia
BRAIN	None	Mild headache Slight lethargy	Moderate headache Great lethargy	Severe headaches Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis Coma
EYE	None	Asymptomatic cataract Minor corneal ulceration or keratitis	Symptomatic cataract Moderate corneal ulceration Minor retinopathy or glaucoma	Severe keratitis Severe retinopathy or detachment Severe glaucoma	Panopthalmitis/ Blindness

LARYNX	None	Hoarseness Slight arytenoid edema	Moderate arytenoid edema Chondritis	Severe edema Severe chondritis	Necrosis
LUNG	None	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency/ Continuous O_2/ Assisted ventilation
HEART	None	Asymptomatic or mild symptoms Transient T wave inversion & ST changes Sinus tachycardia >110 (at rest)	Moderate angina on effort Mild pericarditis Normal heart size Persistent abnormal T wave and ST changes Low ORS	Severe angina Pericardial effusion Constrictive pericarditis Moderate heart failure Cardiac enlargement EKG abnormalities	Tamponade/ Severe heart failure/ Severe constrictive pericarditis
ESOPHAGUS	None	Mild fibrosis Slight difficulty in swallowing solids No pain on swallowing	Unable to take solid food normally Swallowing semi-solid food Dilatation may be indicated	Severe fibrosis Able to swallow only liquids May have pain on swallowing Dilation required	Necrosis/ Perforation Fistula
SMALL/LARGE INTESTINE	None	Mild diarrhea Mild cramping Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement >5 times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/ Perforation Fistula
LIVER	None	Mild lassitude Nausea, dyspepsia Slightly abnormal liver function	Moderate symptoms Some abnormal liver function tests Serum albumin normal	Disabling hepatitic insufficiency Liver function tests grossly abnormal Low albumin Edema or ascites	Necrosis/ Hepatic coma or encephalopathy

KIDNEY	None	Transient albuminuria No hypertension Mild impairment of renal function Urea 25-35 mg% Creatinine 1.5-2.0 mg% Creatinine clearance >75%	Persistent moderate albuminuria (2+) Mild hypertension No related anemia Moderate impairment of renal function Urea>36-60 mg% Creatinine clearance (50-74%)	Severe albuminuria Severe hypertension Persistent anemia (<10g%) Severe renal failure Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance <50%	Malignant hypertension Uremic coma/Urea >100%
BLADDER	None	Slight epithelial atrophy Minor telangiectasia (microscopic hematuria)	Moderate frequency Generalized telangiectasia Intermittent macroscopic hematuria	Severe frequency and dysuria Severe generalised telangiectasia (often with petechiae) Frequent hematuria Reduction in bladder capacity (<150 cc)	Necrosis/ Contracted bladder (capacity <100 cc) Severe hemorrhagic cystitis
BONE	None	Asymptomatic No growth retardation Reduced bone density	Moderate pain or tenderness Growth retardation Irregular bone sclerosis	Severe pain or tenderness Complete arrest of bone growth Dense bone sclerosis	Necrosis/ Spontaneous fracture
JOINT	None	Mild joint stiffness Slight limitation of movement	Moderate stiffness Intermittent or moderate joint pain Moderate limitation of movement	Severe joint stiffness Pain with severe limitation of movement	Necrosis/ Complete fixation

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Glossary

Conventional Radiotherapy technique	This will most frequently be an anterior and posterior parallel opposed field arrangement but there may be situations where a 3 field plan is required. Plans should be with the use of Multi-Leaf Collimators (MLC) and optimisation of fields by physics department.
CTV	Is defined as GTV + 0.5cm. This may need to be extended to take in the complete adjacent vertebrae. It may be appropriate to include areas of microscopic spread as indicated from surgical note and histopathology report.
GTV	The reconstructed tumour volume as seen on the post chemotherapy, pre surgical imaging as well as any immediately adjacent persistently enlarged lymph nodes. The GTV will be trimmed where, following surgery, uninvolved normal organs such as liver or kidney which were previously displaced have returned to their normal positions.
ICRU62	International Commission on Radiation Units and measurements: Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50)
ICRU83	International Commission on Radiation Units and measurements: Prescribing, Recording and Reporting Photon Beam Intensity-Modulated Radiation Therapy (IMRT).
IMAT technique	Radiotherapy for IMAT-Neuroblastoma trial patients is to be delivered with rotational arc therapies (Rapid Arc™, VMAT™ and Tomotherapy™). The methods of treatment planning and delivery must be specified in each centre's process document.
Informed Consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision. Informed consent is documented by means of a written, signed and dated informed consent form.
Interim analysis	An intermediary analysis of clinical trials data, performed at a point at which enough data have been gathered to derive preliminary, but not necessarily complete conclusions. Interim analyses are performed to see whether continuation of a clinical trial is warranted. Results of such an analysis should be seen by the Trial Statistician and Data Monitoring Committee members only.

Interim Clinical Trial / Study Report	A report of intermediate results and their evaluation based on analyses performed during the course of a trial.
Isodose	Isodose curves are the lines joining the points of equal Percentage Depth Dose (PDD). The curves are usually drawn at regular intervals of absorbed dose and expressed as a percentage of the dose at a reference point.
ITV	As the CTV taking into account Internal Motion of the tumour/ tumour bed and adjacent OARs.
Local Control	Absence of progression of tumour at treated site
PTV	CTV + 0.5cm
Related Event	For non-IMP trials a Related Event is defined as an event which resulted from the administration of any of the research procedures.
Unexpected and Related Event	For non-IMP trials an Unexpected and Related Event is defined as an event which meets the definition of both an Unexpected Event and a Related Event.
Unexpected Event	For non-IMP trials the Unexpected Event is defined as the type of event that is not listed in the protocol as an expected occurrence.

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