Radiation versus Observation following surgical resection of Atypical Meningioma: a randomised controlled trial (The ROAM trial)

EORTC protocol 1308

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Study Sponsor(s):

The Walton Centre NHS Foundation Trust
Lower Lane
Fazakerley
Liverpool
L9 7LJ

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CTRC
Clinical Trials Research Centre

EORTC
The future of cancer therapy

NHS
National Institute for Health Research

Protocol Approval

Authorised by Chief Investigator:

Signature: _____ **Date:** 26/08/16

Michael D. Jenkinson PhD, FRCS(Neuro.Surg)
Clinical Senior Lecturer and Honorary Consultant Neurosurgeon
The Walton Centre NHS Foundation Trust
University of Liverpool
Lower Lane
Liverpool
L9 7LJ

Telephone number +44 (0) 151 529 5683
Fax number +44 (0) 151 529 6243

Email:michael.jenkinson@liverpool.ac.uk

Authorised by Lead Statistician:

Signature: _____ **Date:** 30/08/16

Professor Carrol Gamble
Deputy Director
Biostatistics
University of Liverpool
Ground Floor Block F Waterhouse Building
1-5 Brownlow Street
Liverpool
L69 3GL

Authorised on behalf of the Sponsor(s):

Signature: _____ **Date:** 31/Aug/16

Dr Malcolm Steiger
Head of Research, Development and Innovation
The Walton Centre NHS Foundation Trust
Lower Lane
Fazakerley
Liverpool
L9 7LJ
Tel: 0151 529 5533
E-mail: malcolm.steiger@thewaltoncentre.nhs.uk

General Information

This document describes the ROAM trial and provides information about procedures for entering patients into the trial and their continued care throughout the trial. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the Clinical Trials Research Centre (CTRC) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the Chief Investigator via CTRC.

This protocol defines the patient characteristics required for entering the trial and their continued care throughout the trial. Patient recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted.

Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

Statement of Compliance

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, CTU Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

Relationship Statements

The UK Clinical Research Collaboration (UKCRC; www.ukcrc.org) is a partnership organisation working to establish the UK as a world leader in clinical research. Following a review by an international panel, the CTRC at the University of Liverpool has been assessed as reaching the highest quality standard required by the UKCRC and achieved full UKCRC registration.

The CTRC encompasses clinical trials activity in areas including medicines for children, cancer, epilepsy, oral health and obstetrics and gynecology (http://www.ctrc.org.uk/). All CTRC activities are underpinned by methodological rigour, a modern data management system, similar technical requirements and a common set of standard operating procedures.

Contact Details: Institutions

These details can be found in the 'ROAM Institution Contact Details' document provided separately by CTRC.

Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**
Dr Malcolm Steiger Head of Research, Development and Innovation The Walton Centre NHS Foundation Trust Lower Lane Fazakerley Liverpool L9 7LJ Tel: 0151 529 5533 Email:malcolm.steiger@thewaltoncentre.nhs.uk	Mr Michael D Jenkinson Clinical Senior Lecturer and Honorary Consultant Neurosurgeon The Walton Centre NHS Foundation Trust University of Liverpool Lower Lane Liverpool L9 7LJ Tel: +44 (0) 151 529 5683 Fax: +44 (0) 151 529 6243 E-mail: michael.jenkinson@liverpool.ac.uk
Medical Expert who will Advise on Protocol Related Clinical Queries (If other than CI):	**Medical Expert who will Evaluate SAE Reports (If other than CI):**
Mr Mohsen Javadpour, FRCS (Neuro.Surg) Co-chief Investigator Consultant Neurosurgeoon Department of Neurosurgery Beaumont Hospital Dublin 9 Tel: +353 (0) 1 8376727 Fax: +353 (0) 1 8375925 E-mail: mjavadpour@me.com	Dr Brian Haylock, FRCR Consultant Clinical Oncologist Clatterbridge Cancer Centre Bebington Wirral CH63 4JY Tel: +44 (0) 151 482 7851 Fax: +44 (0) 151 482 7675 E-mail: brian.haylock@clatterbridgecc.nhs.uk

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Glossary

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTRC	Clinical Trials Research Centre
CTV	Clinical Target Volume
DFS	Disease Free Survival
DWI	Diffusion Weighted Imaging
EORTC	European Organisation for Research and Treatment of Cancer
FLAIR	(Coronal) fluid-attenuated inversion recovery
GP	General Practitioner
GTR	Gross Total Resection
GTV	Gross Tumour Volume
HES	Hospital Episode Statistics
ICH-GCP	International Conference on Harmonisation Good Clinical Practice
ICRU	International Commission on Radiation Units and Measurements
IDSMC	Independent Data and Safety and Monitoring Committee
IMP	Investigational Medicinal Product
IMRT	Intensity Modulated Radiation Therapy
MDT	Multi-Disciplinary Team
MREC	Multi-centre Research Ethics Committee
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic Resonance Imaging
NCF	Neurocognitive function
NCRI	National Cancer Research Institute
NF-2	Neurofibromatosis type 2
NIHR HTA	National Institute for Health Research Health Technology Assessment programme
OAR	Organs at Risk
ORTA	Online Randomised Trials Access
OS	Overall Survival
PI	Principal Investigator
PISC	Patient Information Sheet/Consent
PRV	Planning Risk Volume
PTV	Planning Target Volume
QALY	Quality Adjusted Life Years
QOL	Quality of Life
R&D	Research & Development
REC	Research Ethics Committee
ROG	EORTC Radiation Oncology Group
RTTQA	Radiotherapy Quality Assurance
SAE	Serious Adverse Event
STR	Subtotal resection
TMG	Trial Management Group
TROG	Trans Tasman Radiation Oncology Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
WRTB	Walton Research Tissue Bank
WHO	World Health Organisation

1 PROTOCOL SUMMARY

Title: Radiation versus Observation following surgical resection of Atypical Meningioma: a randomised controlled trial (The ROAM trial).

Phase: III

Population: The trial will be open to all patients with newly diagnosed atypical meningioma who have undergone gross total surgical resection, and who meet the eligibility criteria.

Inclusion/exclusion criteria:
All patients who are considered for the ROAM trial must fulfil the following criteria:

Inclusion criteria

- Histologically confirmed newly diagnosed solitary atypical meningioma (WHO grade II) based on the 2016 WHO criteria [1]
- Age >/= 16 years
- All anatomical locations allowed except optic nerve sheath tumour
- Complete resection (Simpson 1, 2 or 3) as assessed by the surgeon
- Able to commence radiotherapy within 12 weeks of surgery
- WHO performance status 0, 1 or 2 (see Appendix 1)
- Women of reproductive potential must use effective contraception for the whole duration of the treatment
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

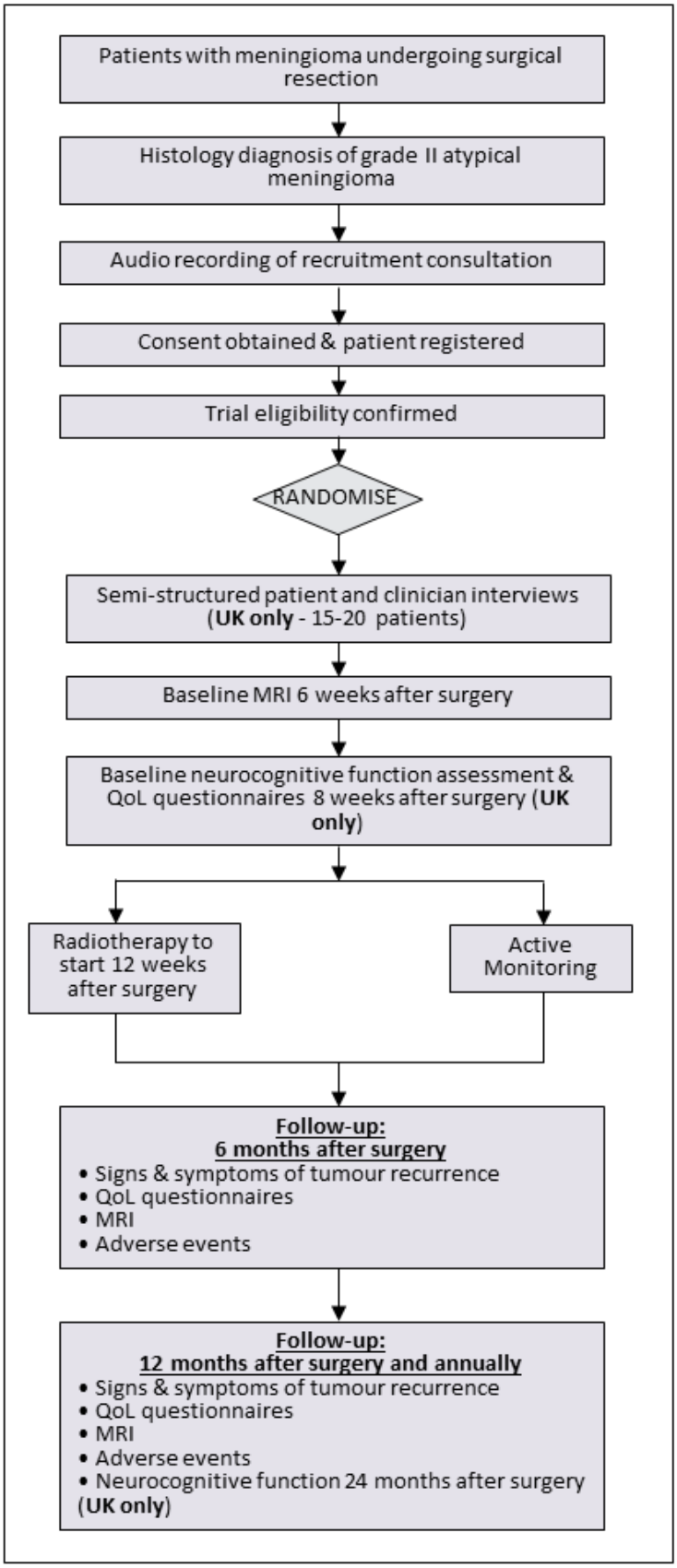
Exclusion criteria

- Neurofibromatosis type II (NF-2)
- Optic nerve sheath tumours
- Multiple meningiomas
- Radiation-induced meningioma
- Clinical evidence of second malignancy, except for cervix carcinoma in situ or basal cell carcinoma, and history of invasive malignancy unless treated with curative intent and the patient has not been disease free for the last five years
- Previous intracranial tumour
- Pregnant or lactating women

Study Centres and Distribution:	International multicentre European study, to be conducted in collaboration with European Organisation for Research and Treatment of Cancer (EORTC). Patients will be recruited from neurosurgical and oncology units in the UK in the first instance, and throughout Europe with EORTC centres and Australia/New Zealand with the Trans Tasman Radiation Oncology Group (TROG) at a later date.
Study Duration:	The trial will aim to recruit 190 patients over a period of 44 months, with approximately 118 patients to be recruited in the UK, however there will be no limit on the number of patients that either the UK sites, EORTC or TROG sites may recruit within the overall trial target. Patients will be followed up for a minimum of 5 years post surgery.
Description of Agent/ Intervention:	ROAM will be a two-arm, multi-centre, randomised controlled trial. The trial will randomise patients who have undergone gross total surgical resection of atypical (grade II) meningioma to receive either early adjuvant fractionated radiotherapy for 6 weeks (intervention) or active monitoring (comparator). This will be a 2-stage trial (both stages will run in parallel): • Stage 1 (feasibility and acceptability): this stage is designed to maximise recruitment. This is a rare condition and therefore it is important to maximise patient and clinician acceptability thereby optimising recruitment and retention. A qualitative study will be embedded within this stage of the trial (UK sites only) to achieve these goals. Patients wishing to continue will proceed to randomisation (stage 2). • Stage 2 (randomisation): patients who wish to participate in the trial will be randomised in a 1:1 ratio to either early radiotherapy or active monitoring.
Primary Objective:	To determine whether early adjuvant fractionated external beam radiotherapy reduces the risk of tumour recurrence or death due to any cause compared to active monitoring in newly diagnosed atypical meningioma
Secondary Objective/s:	• To assess the early and late effects of fractionated radiotherapy • To assess and compare quality of life in patients with atypical meningioma according to treatment arm • To assess and compare the neurocognitive function in patients with atypical meningioma according to treatment arm • To record the second line treatments (surgery, radiotherapy, radiosurgery) used at tumour recurrence according to treatment arm • To determine overall survival (OS) at 5 years

- To assess the cost-effectiveness of adjuvant radiotherapy compared to active monitoring
- To correlate proliferation rate and molecular characteristics with time to tumour recurrence (separate funding will be sought)

Schematic of study design:



2 BACKGROUND INFORMATION

2.1 Introduction

Atypical meningioma is an intermediate grade brain tumour that arises from the linings of the brain. They tend to affect adults with a peak incidence at age 40-60 years [1]. The 5-year tumour recurrence rates are reported as between 39 and 58% [2-6]. The primary treatment for atypical meningioma is surgical resection. In patients with residual solid tumour, radiotherapy is administered to reduce the risk of recurrence. In patients with gross total resection the role of radiotherapy has not been defined and the options of early radiotherapy or active monitoring are discussed with the patient. Some clinicians give early radiotherapy, whilst others advise active monitoring with radiotherapy given only at recurrence. Whilst radiotherapy has been shown to be an effective adjuvant treatment in some studies [2,3], but not others [4-6], there is no consensus as to which of these approaches is best.
The use of radiotherapy may obviate the need for further surgical procedures, but must be balanced against the potential risks of radiotherapy, which include neurocognitive impairment, hypopituitarism and radiation-induced tumours. Tumour recurrence can also affect neurocognitive function (NCF) and quality of life (QoL). Tumours that recur can be treated with further surgery and radiotherapy.

The trial will recruit 190 patients with newly diagnosed atypical meningioma who have undergone gross total resection. Patients will be randomised to either early adjuvant fractionated radiotherapy (intervention) or active surveillance (comparator) and followed up for a minimum of 5 years. An embedded qualitative study will implement bespoke strategies to maximise recruitment to ROAM and ensure successful delivery of the trial [7]. The primary outcome will be time to MRI evidence of recurrence (disease free survival). Secondary outcomes will include overall survival, neurocognitive function and quality of life, time to second line tumour treatment and health economic analysis.

2.2 Rationale

Meningiomas comprise 25-33% of adult primary brain tumours. The WHO [1] classify 3 grades:

- Benign (grade I) meningioma (~90%)
- Atypical (grade II) meningioma (~7%)
- Anaplastic (grade III) meningioma (~3%)

The annual UK incidence of atypical meningioma is 0.2-0.5 / 100,000 / year and ~150 undergo surgical resection each year. Since the publication of the 2000 WHO classification, the reported incidence of atypical meningioma has risen to 20-35% [5,8,9], nevertheless they remain very rare. The primary treatment for symptomatic or enlarging atypical meningioma is surgical excision and completeness of resection is an important prognostic factor [10]. Simpson defined extent of resection into 5 categories:

- Simpson 1: complete tumour removal, including dural attachment and any abnormal bone
- Simpson 2: complete tumour removal, with coagulation of dural attachment
- Simpson 3: complete tumour removal, without resection or coagulation of its dural attachment
- Simpson 4: partial tumour removal
- Simpson 5: biopsy only

In modern neurosurgery Simpson 1-3 constitute gross total resection (GTR), and Simpson 4-5 constitute subtotal resection (STR).

Benign (grade I) meningioma have a low risk of recurrence (~10% at 5 years) following surgical resection and are managed by active monitoring with MRI scans. Adjuvant radiotherapy is indicated for anaplastic (grade III) meningioma to prolong time to recurrence however 5-year progression free survival is only ~10% [11].
The role of radiotherapy in atypical (grade II) meningioma after gross total resection has not been defined. Some retrospective studies have reported a reduced recurrence rate with adjuvant radiotherapy [2,3], however other studies have reported that radiation does not reduce recurrence rate [4-6]. A recently published systematic review concluded that since atypical meningioma preferentially recur within 5 years, future studies should investigate the role of early adjuvant radiotherapy in these patients [12]. **There have been no randomised controlled trials in this tumour population.** Currently the treatment decision for adjuvant radiotherapy varies according to patient, surgeon and neuro-oncologist preference [13,14], and some European expert opinion recommends that all atypical meningioma patients should have radiotherapy (www.meningiomauk.org). There is no agreement on the current standard of care for patients with atypical meningioma. The mainstay of treatment is surgical resection, aiming for gross total resection. In patients where there is residual solid tumour adjuvant radiotherapy is recommended to reduce the risk of tumour progression. In patients with gross total resection the options of early radiotherapy or active monitoring are discussed with the patient. Some clinicians give early radiotherapy, whilst others advise active monitoring with radiotherapy given only at recurrence. There is no consensus as to which of these approaches is best. The recently closed EORTC study 22042-26042 was non-randomised dose-escalation study that investigated postoperative adjuvant high-dose radiotherapy following both gross total and subtotal resection of atypical and anaplastic meningioma. This phase-II and observation study (n=77) is scheduled to report in 2016, however the results from this trial will not inform policy on best management of completely resected atypical meningioma since there was no comparator arm of observation only.
The treatment aim for patients with atypical meningioma is local tumour control, since tumour recurrence has a major impact on patient outcome. Although meningiomas have been considered as radio-resistant, radiotherapy has been shown to be an effective adjuvant treatment in some trials [2,3], but not others [4-6]. The use of radiotherapy may obviate the need for further surgical procedures, but must be balanced against the potential risks of radiotherapy, which includes neurocognitive impairment, hypopituitarism and radiation-induced tumours. Equally in patients who are managed with observation, tumour recurrence itself can also affect neurocognitive function (NCF) and quality of life (QoL). A standardized battery of NCF tests, have been shown to be sensitive for assessing the impact of both brain tumours and treatment effects in prospective trials [15-17]. Neurocognitive function has been shown to independently predict survival for brain tumour patients and predicts tumour progression [18,15,17]. It is therefore important to assess the impact of adjuvant radiotherapy on the NCF and QoL of atypical meningioma patients, compared to active monitoring, and determined whether the therapeutic ratio favours immediate adjuvant radiotherapy in completely resected atypical meningioma patients.

2.3 Objectives

Primary objective:

To determine whether early adjuvant fractionated radiotherapy reduces the risk of tumour recurrence or death due to any cause compared to active monitoring in newly diagnosed atypical meningioma.

Secondary objectives:

- To assess the early and late effects of fractionated radiotherapy

- To assess and compare quality of life in patients with atypical meningioma according to treatment arm
- To assess and compare the neurocognitive function in patients with atypical meningioma according to treatment arm
- To record the second line treatments (surgery, radiotherapy, radiosurgery) used at tumour recurrence according to treatment arm
- To determine overall survival (OS) at 5 years
- To assess the cost-effectiveness of adjuvant radiotherapy compared to active monitoring (UK sites only)
- To correlate proliferation rate and molecular characteristics with time to tumour recurrence (separate funding will be sought).

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

The potential toxicity associated with radiotherapy delivered to the brain is not inconsequential and includes, but is not limited to, cognitive impairment, hypopituitarism and radiation-induced tumours. The disease itself and its recurrence requiring multiple surgical procedures may produce similar impairments. Specific neurocognitive tests and quality of life assessments will therefore be used in this study to document and monitor these effects. In the very rare instance that a patient experiences loss of capacity during radiotherapy, it will be at the clinicians' discretion to treat the cause of this and, if thought to be in the patients' best interest, continue with radiotherapy.

2.4.2 Known Potential Benefits

There are no known benefits to patients taking part in the ROAM trial.The trial will establish the role of early adjuvant fractionated radiotherapy for patients who have undergone gross total resection of atypical meningioma.

3 SELECTION OF CENTRES

Sites within the UK and Ireland will be identified via the National Cancer Research Institute (NCRI) Brain Tumour Clinical Studies Group and Society of British Neurological Surgeons networks. Within mainland Europe the EORTC will identify suitable sites to participate in the trial. Sites will be identified and chosen if they meet all the requirements for participation in the trial.

UK study centres will be initiated once all global (e.g. local R&D approval) and study-specific conditions (e.g. training requirements) have been met, and all necessary documents have been returned to CTRC.

Within mainland Europe, the EORTC will authorise sites for patient recruitment after completion of all applicable national legal and regulatory requirements and after receiving all necessary documents at EORTC.

For Australia and New Zealand, the TROG will authorise sites for patients recruitment after completion of all applicable national legal and regulatory requirements and after receiving all necessary documents at the CTRC and EORTC.

3.1 Centre Inclusion Criteria

a. Has a neuro-oncology/neuroscience multidisciplinary team (MDT) or tumour board meeting
b. Has access to neuropsychology service (UK sites only)
c. Assess and offer neurosurgery to patients with atypical meningioma
d. Assess and offer fractionated radiotherapy to patients with atypical meningioma using modern radiotherapy planning techniques (e.g. intensity modulated radiation therapy [IMRT]). This can be at the same site as the neurosurgery service or at a separate centre.

3.2 Centre Exclusion Criteria

a. Not meeting the inclusion criteria listed above.

4 TRIAL DESIGN

A two-arm, multi-centre, randomised controlled trial to compare radiotherapy versus observation in patients who have undergone gross total surgical resection (Simpson 1-3) of atypical (grade II) meningioma.

4.1 Primary Endpoint

Time to MRI evidence of tumour recurrence or death due to any cause (disease free survival [DFS]).

4.2 Secondary Endpoint(s)

- Toxicity of radiotherapy assessed by CTCAE (Common Terminology Criteria for Adverse Events)
- Quality of life
- Neurocognitive function (UK sites only)
- Time to second line (salvage) treatment (surgery, radiotherapy, radiosurgery)
- Time to death (overall survival [OS])
- Health economic analysis (incremental cost per QALY gained) (UK sites only)

Disease free survival (DFS) will be counted from the date of surgery until the date of MRI evidence of tumour recurrence or death due to any cause. Only clear dural thickening as identified by the investigator is to be considered tumour.

Overall survival (OS) will be counted from the date of surgery until death due to any cause.

5 STUDY POPULATION

5.1 Inclusion Criteria

Patients with the following characteristics will be eligible for inclusion in the trial:

a) Histologically confirmed newly diagnosed solitary atypical meningioma (WHO grade II) based on the 2016 WHO criteria [1]
b) Age >/= 16 years
c) All anatomical locations allowed except optic nerve sheath tumour
d) Complete resection (Simpson 1, 2 or 3) as assessed by the surgeon
e) Able to commence radiotherapy between within 12 weeks of surgery (ideally 8-12 weeks)
f) WHO performance status 0, 1 or 2 (Appendix 1)
g) Women of reproductive potential must use effective contraception for the whole duration of the treatment
h) Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

5.2 Exclusion Criteria

Patients with the following characteristics will be excluded from the trial:

a) Neurofibromatosis type II (NF-2)
b) Optic nerve sheath tumours
c) Multiple meningiomas
d) Radiation-induced meningioma
e) Clinical evidence of second malignancy, except for cervix carcinoma in situ or basal cell carcinoma, and history of invasive malignancy unless treated with curative intent and the patient has not been disease free for the last five years
f) Previous intracranial tumour
g) Pregnant or lactating women.

5.3 Patient Transfer and Withdrawal

In consenting to the trial, patients are consented to trial treatment, follow-up and data collection. If voluntary withdrawal occurs, the patient should be asked to allow continuation of scheduled evaluations and to complete an end-of-study evaluation if appropriate.
Follow-up of these participants will be continued through the trial Research Nurses, the lead investigator at each centre unless the participant explicitly also withdraws consent for follow-up.

5.3.1 Participant Transfers

For participants moving from the area, every effort should be made for the participant to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the participant or for follow-up via GP in the UK.

A copy of the participants CRFs should be provided to the new site. The participant will have to sign a new consent form at the new site, and until this occurs, the participant remains the responsibility of the original centre. The CTRC should be notified in writing of participant transfers for UK sites, the EORTC should be notified in writing for EORTC sites and the TROG should be notified in writing for TROG sites.

5.3.2 Withdrawal from Trial Intervention

Participants may be withdrawn from treatment for any of the following reasons:

a. The participant withdraws consent.
b. Any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion.

If a participant wishes to withdraw from trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up (see section 5.3.3).

5.3.3 Withdrawal from Trial Completely

Participants are free to withdraw consent at any time without providing a reason. Participants who wish to withdraw consent for the trial will have anonymised data collected up to the point of that withdrawal of consent included in the analyses. The patient will not contribute further data to the study; the trial team should be informed in writing and a withdrawal CRF should be completed. Data up to the time of withdrawal will be included in the analyses unless the patient explicitly states that this is not their wish. If it is the wish of the patient to have their data excluded in its entirety, a CRF for destruction of existing data will be completed.

6 ENROLMENT AND RANDOMISATION

6.1 Screening

Patients will be screened for eligibility after undergoing gross total resection surgery for atypical meningioma. Potentially eligible patients will be identified at the neuro-oncology/neuroscience MDT or tumour board meeting.

A 'Screening log' will be maintained of all patients with newly diagnosed atypical meningioma who undergo surgical resection. Reasons for ineligibility (e.g. incomplete resection, previous cranial irradiation etc.) will be recorded. Reasons for declining to participate will be asked routinely, but it will be made clear that patients do not have to provide a reason unless happy to do so.

6.2 Consent

Eligible patients will be approached to participate in the trial and their informed consent will be sought.

6.2.1 Qualitative study (selected UK sites only)

The qualitative study will be undertaken in selected UK sites according to geographical considerations. The qualitative study aims to improve the patient experience in participating in clinical trials.

6.2.1.1 Overview of qualitative study

As part of a qualitative study embedded within ROAM, the permission of patients will be sought to audio-record consultations during which patients are approached for recruitment to the trial. The qualitative study, which will run during the pilot phase of ROAM, will examine how information about the trial is exchanged by clinicians and patients as they discuss ROAM and consent is sought. As well as the audio-recordings of the recruitment consultations, a sub-sample of patients and clinicians will subsequently be interviewed by a qualitative researcher. The qualitative study will draw on previously described methods [19-21] to identify the source of any recruitment difficulties and design bespoke strategies to optimise recruitment. This approach has demonstrated success in enhancing recruitment in previous trials [22] and aims to improve the patient experience by improving information exchange and communication. Specifically, the qualitative study will compare discussions during recruitment consultations, with clinicians' and patients' interpretations of these consultations. The qualitative study team will use these comparisons to identify factors associated with recruitment difficulties and will work closely with the trial team, centres and PPI representative to develop and implement strategies to enhance recruitment to ROAM, including advice or training for clinicians on explaining the study to patients to optimise recruitment and that patients are supported in making an informed decision about ROAM.

6.2.1.2 Audio-recordings patient-clinician consultations about ROAM for qualitative study

Collection of audio-recordings of consultations for the qualitative study will be facilitated by clinicians and research nurses at those ROAM centres participating in the qualitative study. Clinicians and research nurses will *routinely* seek permission to audio-record recruitment consultations from all patients who they intend to approach about ROAM. Before discussing ROAM, clinicians will briefly advise patients that they will be discussing a clinical research study and if the patient permits, they would like to record the consultation to inform communication with patients about research studies. If verbal permission for audio-recording is declined, the recruitment consultation will not be audio-recorded. If permission is given, the clinician or research nurse will activate an audio-recorder and discussion of the trial will proceed as usual. At the end of the consultation about ROAM, the clinician or research nurse will briefly outline the qualitative study and seek the patient's consent for the audio-recording to be passed to the qualitative study team. If consent is declined the audio-recording will be immediately erased. If consent is given, clinicians/research nurses will upload the audiorecording to either: (1) a confidential and secure on-line service (e.g. Voicescript), whereby the recording will be accessible to the researcher; or (2) an encrypted flash drive, which will be sent to the qualitative research team; the appropriate method of data transfer will be determined by the facilities available at each of the NHS sites. As noted above, all consultations at centres participating in the qualitative study will be audio-recorded (provided patients give permission; previous experience suggests approximately 90% of patients permit audio-recording). It is expected that sampling of consultations will continue until saturation is reached, which is anticipated will require 25-35 audio-recorded consultations. Sampling for the qualitative study will also be informed by the developing analysis.

6.2.1.3 Interviews for qualitative study

At the end of the consultation clinicians/research nurses will inform patients about the opportunity to take part in qualitative interviews and seek the patient's verbal permission for the qualitative researcher to contact the patient about these interviews (the qualitative researcher will seek the patient's written consent for the interviews at a later date). As the qualitative study is focussed on the experience of communication about research (i.e. whether or not a patient consents to ROAM), clinicians/research nurses will invite all patients who have been approached about ROAM to be interviewed. Patients' details (name, address, telephone numbers, email address, age and gender) along with details of the recruitment consultation (clinician's contacts details, date of consultation recrding (if applicable) and whether or not consent was obtained for ROAM) will be recorded on a pro forma for the qualitative study. These pro formas will be placed in stamped addressed envelopes and clinicians/research nurses will post them to the qualitative researcher. Copies of the consent forms for audio recordings will also be returned to the qualitative researcher in this way; site staff will be advised to post pro formas and consent forms separately. Alternatively, these documents can be faxed directly to the qualitative researcher. It will be made clear to patients that participation in the qualitative study is voluntary and that only some patients will be selected to participate in the qualitative interviews. The qualitative researcher will contact selected patients to arrange interviews, usually within 1-3 weeks of the audio-recorded discussion and before initiation of allocated treatment (observation or radiotherapy). It is anticipated that most patients will be interviewed face-to-face in their own homes, although they will be able to opt for a telephone interview or to be interviewed in

another place of their choosing. All patients who express an interest in taking part in the qualitative interviews but are not selected for interview will be contacted by letter to thank them for their interest. Clinicians involved in discussing ROAM with patients will also be invited to participate in qualitative interviews about their experiences and views of recruiting patients to the trial.

Sampling of interviewees will aim for maximum diversity (e.g. sampling will encompass variations in the style of consultation, patients who decline as well as those who consent, patients randomised to observation as well as those randomised to radiotherapy; sampling of clinicians will include surgeons and oncologists and encompass variation in centre recruitment activity and how clinicians explain the trial to patients). Sampling will also aim for data saturation, which is anticipated will require 15-20 patient and 10-15 clinician interviews. It is anticipated that most participants sampled for interview will be those patients and clinicians who have had audio-recorded consultations, although others may be sampled where they have valuable perspectives to contribute. All interviews will be conducted by a researcher with proven skills in qualitative interviewing and managed with sensitivity. Topic-guided semi-structured qualitative interviews will explore participants' experiences and views of the recruitment process and the information exchanged. Interviews will be conversational and participant-centred and participants will be free to decline to answer any questions or to stop the interviews at any point. Interviews with clinicians and patients may be facilitated by playback of selected excerpts of consultations, where this is helpful and clinicians and patients agree.

6.2.1.4 Qualitative analysis of audio-recorded consultations and interviews

Audio-recordings of consultations will be transcribed, checked and anonymised ready for analysis; analysis of consultations will also involve listening to audio-recordings to take account of the subtleties of the tone and intonation of speech. Analysis will draw on a combination of content analysis, interpretive thematic analysis [22] and elements of conversational analysis and be assisted by qualitative analysis software. The design, conduct and analysis of the qualitative study will use procedures to support quality in qualitative research [23], including systematic data coding, triangulation and exceptional case analysis.

6.2.1.5 Qualitative research recruitment logs

Recruitment logs at centres participating in the qualitative study will record all patients:

a. eligible to be approached about ROAM and actually approached about ROAM, or reasons not approached
b. verbal permission sought for audio-recorded consultation and whether permission given or not
c. consented or declined for the audio-recorded consultation to be passed to the qualitative research team
d. permission sought for the qualitative researcher to contact them for interview and whether permission was given or not

In addition, the qualitative researcher will maintain a log of all patients and clinicians eligible to be interviewed, and those who were invited to be interviewed (and why), whether they accepted or declined and the number who went on to be interviewed. The qualitative

researcher will liaise with trial teams to ascertain for each consultation recording and patient eligible for interview:

a. whether the patient consented to be randomised within ROAM or declined randomisation and in which case whether s/he opted for observation or radiotherapy
b. whether a patient withdrew from ROAM post randomisation at any stage prior to initiation of allocated treatment (observation or radiotherapy) and in which case whether s/he opted for observation or radiotherapy.

6.3 Randomisation

Informed consent must be obtained before enrolment and any trial-specific tests.
A participant can only be randomised after verification of eligibility. Both the eligibility check and randomisation must be done before the start of the protocol treatment.

Participant randomisation will only be accepted from authorised investigators.

Participants should be randomised directly on the **EORTC online randomisation system** (ORTA) accessible 24 hours a day, 7 days a week, through the internet. To access the interactive randomisation programme, the investigator needs a username and a password (which can be requested at http://orta.eortc.be/ and provided by EORTC).

In case of problems, investigators can phone the EORTC call centre from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday to receive any help on the system and/or to randomise participants. In this case, the call centre will connect to the EORTC randomisation website and go through all selection criteria with the site over the phone. Randomisation via the EORTC call centre is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (http://orta.eortc.be/) and it is updated annually.

Through internet:	http://orta.eortc.be/
In case of problems, randomisation via EORTC call centre:	*+32 2 774 16 00*

STANDARD INFORMATION REQUESTED:

- institution number
- protocol number: 1308
- step number: 1 *(randomising a patient via ORTA is step 1 in all cases for this trial, no other step is foreseen)*
- name of the responsible Investigator
- patient's code (*maximum 4 alphanumerics, a unique code to help identify the patient within the institution*)
- patient's birth date (*day/month/year*)

PROTOCOL SPECIFIC QUESTIONS:

- all eligibility criteria will be checked one by one
- actual values for the eligibility parameters will be requested when applicable
- date of written informed consent (*day/month/year*)

Once eligibility has been verified, treatment will be randomly allocated to the patient, together with a **sequential patient identification number ("seqID")**. This number will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms.

6.4 Baseline

Following randomisation, participants in both arms will undergo a baseline post-operative MRI 6 weeks after surgery. It is accepted that some patients may have already undergone an early post-operative MRI scan (i.e. within 72 hours), however the MRI should still be performed 6 weeks after surgery. Neurocognitive function (NCF) will be tested 8 weeks after surgery (UK participants only). Adjuvant radiotherapy will commence approximately 12 weeks after surgery. Table 1 describes the visit windows for each baseline assessment.

A medical/neurosurgical history will be taken and recorded on the appropriate CRF. Separate sections will record presenting symptoms and duration and co-morbidities. Patient performance status and symptom-directed physical and neurological examination will be recorded.

7 TRIAL TREATMENTS

7.1 Introduction

Patients in both arms will typically have an early post-operative follow-up approximately 2 weeks of resection surgery to discuss the histopathology results and assess wounds and clinical status: - trial eligibility will be established at this stage and patients invited to participate. Follow-up thereafter would be at 6 months, 12 months and annually until tumour recurrence, death or trial closure. EORTC C30 and BN20 quality of life (appendix 2; all sites), EQ-5D-5L health outcome, and resource use questionnaires will be administered at each follow up visit. All participants will be followed up for a minimum of 5 years post-surgery. At the time of recruitment, all patients will be asked to additionally consent to be contacted for longer term follow up (separate funding will be sought for a long-term outcome study).

7.2 Arm A: Radiotherapy

7.2.1 Equipment & Planning

Radiotherapy will be planned and delivered with modern techniques, including but not limited to IMRT and volumetric modulated arc therapy. Detailed outlining and planning guidelines are provided in a separate Quality Assurance pack available from the National Radiotherapy Trials Quality Assurance Group (RTTQA). An approved accreditation system, including benchmark outlining and planning cases, and real time review will be employed.

7.2.2 Immobilisation

All particpants will be immobilised in a customised thermoplastic shell or relocateable stereotactic frame in a supine position unless the meningioma was in an occipital location, in which case a prone treatment position is permitted.

7.2.3 Data acquisition and Definitions of Target Volumes & Organs at Risk

The definition of volumes will be in accordance with the International Commission on Radiation Units and Measurements (ICRU) Report #50 [23] and ICRU Report #62 [24]. Volumes will be defined based on a volume MRI scan (T1+Gad) taken 2-8 weeks post-operatively and co-registered to a computerised tomography (CT) scan. The CT scan should use IV contrast and must have a maximum 3mm slice spacing. The CT scan should extend from above the vertex to below the thyroid. The pre-operative MRI will also ideally be co-registered and used to guide the volume definition.

7.2.3.1 Gross Tumour Volume (GTV)

The GTV is defined as the resection cavity on the post-operative MRI and planning CT-scan. If bone is involved, a CT bone window setting is strongly advised. Clearly thickened dural tails and hyperostotic bones should be included whereas non-enhancing but thickened dura does not need to be included.

7.2.3.2 Clinical Target Volume (CTV)

The CTV is defined as the GTV together with sub-clinical microscopic tumour which may include the pre-operative tumour bed, peritumoural oedema, hyperostotic bone changes,

and dural enhancement or thickening as seen in the CT/MRI at diagnosis. An additional 3-dimensional margin of 10 mm along the meninges should be added limited by the participant skin surface. The margin should be reduced to 5mm where this would extend into brain tissue unless there is evidence of invasion when the 10 mm margin should be maintained.

7.2.3.3 Planning Treatment Volume (PTV)

The PTV is is defined as the CTV plus an isotropic 5 mm margin, to account for day to day setup variation related to the ability to immobilize the participant. If high precision radiotherapy techniques are used the PTV margin will be reduced to 3mm. The PTV should not extend outside the participant.

7.2.3.4 Organs at Risk (OAR)

OAR include the following normal tissue volumes: eyes - the lens, optic nerves and chiasm (optic apparatus) and the globe (includes anterior and posterior chambers); brainstem; pituitary; cochlea; lacrimal glands; skin (a 5 mm thick rind) and the uninvolved brain.

7.2.4 Treatment planning

IMRT (or similar modern techniques) may be planned using fixed fields or arcs. The treatment plan to be used for each participant is based on an analysis of volumetric doses including the dose volume histogram (DVH) of the PTV and the OARs. Treatment planning should conform to ICRU 50, 62 and 83 rules for coverage of GTV, CTV and PTV (ICRU 1993, ICRU 1999, ICRU 2010) [23-25] as defined in the planning guidelines. Additionally, organs at risk (OAR) detailed in 7.2.3.4 should be delineated according to the ICRU 62 rules [24], and constraints applied as listed in 7.2.7. OAR planning risk volumes (PRV) should be defined by applying a margin to the PRV as defined in the planning guidelines.

7.2.5 Target dose

7.2.5.1 Prescription point

Dose prescription will be to the median dose to the PTV ($D_{50\%}$) as recommended by ICRU report 83 [25] which, for 3DCRT plans, approximates to the dose at the centre of the target volume.

7.2.5.2 Dose definition

The absorbed dose is specified as Gy-to water.

7.2.5.3 Tissue heterogeneity

Inhomogeneity correction for bone and soft tissue density variation will be applied according to standard international practice.

7.2.5.4 Prescribed dose and fractionation

- The prescribed dose is 60Gy in 30 fractions to the median (or mean) of the PTV dose.
- The CTV should receive a minimum of 57 Gy
- Dose homogeneity requirements in the PTV shall be -5% to +7%.
- The PTV should be encompassed by the 95% isodose, but the 90% isodose is acceptable in close proximity to OAR
- All radiation should be given at 2 Gy fractions, one fraction per day, five fractions per week.

- Radiotherapy delays (gaps policy): Delays in RT should be avoided. If a treatment gap occurs two fractions per day should be avoided and an additional fraction at the weekend is encouraged. If a treatment gap occurs due to toxicity an Adverse Event form should be completed.

7.2.6 Normal tissue sparing

It is important to minimize the dose to the PRVs whenever possible. This must be weighed against the possibility of sub-optimal treatment of the target volume.

7.2.7 Dose calculation and reporting

Isodose distributions will be calculated in 3 dimensions considering the dose distribution in transverse, coronal and sagittal planes. Recording of integral doses to GTV, CTV, PTV and OARs with dose volume histograms is mandatory.

7.2.8 Timing of radiotherapy

Treatment with radiotherapy should start within 12 weeks of surgery (and ideally within 8-12 weeks). Participants will receive radiotherapy for 6 weeks, delivered daily from Monday to Friday.

7.2.9 Radiotherapy Quality Assurance (QA)

Treatment centres must be accredited for IMRT treatment (or similar modern techniques) by the NCRI RTTQA RTQ EORTC groups.

7.2.9.1 The Quality Assurance Programme

The Quality Assurance programme will be defined by the UK National RTTQA and EORTC RTQA groups and will be detailed in the QA pack document. This programme will comprise the following:

7.2.9.1.a Facility Questionnaire
7.2.9.1.b: Outlining and planning benchmark cases (**EORTC: Benchmark Cases**)
7.2.9.1.c Case reviews (**EORTC: ICR**)
7.2.9.1.d IMRT or similar modern technique credentialing

7.3 Arm B: Observation

Participants will not receive radiotherapy but will have the same schedule of follow-up assessments as patients randomised in Arm A.

7.4 Concomitant Medications/Treatments

7.4.1 Medications Permitted

All medications are permitted before and during the trial.

7.4.2 Medications Not Permitted/ Precautions Required

There are no contra-indicated medications.

7.4.3 Data on Concomitant Medication

Data will be collected on use of corticosteroids (e.g. dexamethasone), anti-epileptic drugs and anti-emetics. Start date and end of therapy will be recorded.

7.5 Co-enrolment Guidelines

Individuals who have participated in a trial testing a medicinal product prior to screening for ROAM may be eligible for the ROAM trial and should be discussed with the Chief Investigator. Following randomisation into the ROAM trial, where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the ROAM trial, this must first be discussed with the coordinating centre (CTRC/EORTC/TROG as applicable) who will contact the Chief Investigator.

8 ASSESSMENTS AND PROCEDURES

8.1 Schedule for Follow-up

All electronic CRFs should be completed as described in section 13.3 by personnel named on the delegation log as authorised to do so, usually the research nurse, and returned within 4 weeks of visit date, unless stated otherwise. Participating sites will be expected to each maintain a file of essential trial documentation (Investigator Site File), which will be provided by CTRC/EORTC/TROG (as applicable).

Once written informed consent has been obtained from the patient, the research team will collect baseline characteristics using the baseline CRF and the patient will be randomised and followed-up in the trial. For screening and randomisation procedures refer to section 6.1 and 6.3 respectively. For details of procedures associated with trial treatments refer to Table 1.

Patient details including name, initials, date of birth and randomisation number (Seqid) will be reported on the consent form, separate to clinical data; consent will also be sought for patients to be contacted for long term follow-up outside the trial.

Table 1

Time (weeks/months)		2 weeks after surgery	3 weeks after randomisation	6 weeks after surgery	8 weeks after surgery	12 weeks after surgery	6 months after surgery	12 months after surgery	24 months after surgery	36 months after surgery	48 months after surgery	60 months after surgery	
Visit window		Up to 5 weeks post-surgery	At any time from randomisation and up to 12 weeks after surgery (must be prior to commencement of RT where applicable)	2 - 8 weeks after surgery (must be prior to commencement of RT where applicable)	4 - 10 weeks after surgery (must be prior to commencement of RT where applicable)	8 - 12 weeks after surgery	± 1 month	± 1 month	± 1 month	± 1 month	± 1 month	± 1 month	
	Screening	Consent/ Randomisation/ Baseline	Semi-structured interviews	Baseline MRI	Baseline NCF and QoL							End of trial	Premature withdrawal
Informed consent		X											
Semi-structured interviews[b]			X										
Eligibility criteria assessment	X	X											
Medical History review		X											
Concomitant medicines review		X				X	X	X	X	X	X	X	X
Pregnancy test		X											
Randomisation		X											
Study intervention						X							
Physical exam – symptom directed		X											
MRI scans	X[c]			X			X	X	X	X	X	X	X
Assessment of Adverse events						X[a]	X	X	X	X	X	X	X
Assessment of time to MRI evidence of tumour recurrence/progression (primary outcome)							X	X	X	X	X	X	X
Time to Second line treatment							X	X	X	X	X	X	X
Quality of life (QoL) questionnaire-EQ5D5L[b]					X		X	X	X	X	X	X	X
QoL questionnaire–EORTC C30					X		X	X	X	X	X	X	X
QoL questionnaire–EORTC BN20					X		X	X	X	X	X	X	X
Neurocognitive function assessments[b])					X				X				
Tumour tissue for biobanking					X								
Serum sample for biobanking[b]				X			X	X	X	X	X	X	X
Resource use questionnaire[b]					X		X	X	X	X	X	X	X

[a] Radiotherapy arm only, [b] UK sites only, [c] Baseline pre-operative MRI form

8.2 Procedures for assessing Efficacy

The primary outcome is disease free survival (DFS). This will be assessed on MRI at 6, 12, 24, 36, 48 and 60 months post surgery, using the following sequences:

- Axial T2 SE
- T1 axial SE
- Coronal FLAIR (fluid-attenuated inversion recovery) - with fat saturation
- Diffusion Weighted Imaging (DWI)
- T1+gadolinium volume (1mm slices)

Tumour recurrence will be defined as evidence of new contrast enhancing solid tumour (including dural thickening), and will be assessed locally by the treating clinical team and recorded in the appropriate CRF. All follow-up MRI scans will be anonymised and sent to the trial sponsor (The Walton Centre) for central review. Central review will be performed in batches. In addition, the pre-operative MRI will also be requested for transfer.

8.3 Procedures for Assessing Safety

Early and late adverse events associated with radiotherapy will be recorded in the appropriate CRF. Data including (but not limited to) skin reactions, hair loss, wound breakdown, fatigue, headache, leucoencephalopathy, pituitary dysfunction and cognitive decline will be recorded.

8.4 Other Assessments

8.4.1 Health Economics (UK sites only)

There are no existing economic studies of treatment options in atypical meningioma and to assess the balance of the potential benefits of reduced recurrence rates against the costs, we will conduct a cost utility analysis, from the perspective of the NHS.

Resource use will be based on entries made in designated sections of patients' case report forms, Hospital Episode Statistics data sourced from the Health and Social Care Information Centre for patients recruited in England, and data from hospital Patient Administration Systems. Trial nurses will complete the questionnaires with patients during follow up visits.

- The CRF will be used to record data on procedures and interventions as well as dates of patient transfers both within and between hospitals from admission to discharge.
- Six months after randomising the last patient at each recruiting centre, the Finance departments of each centre will be contacted, and a request submitted for: Ward name; ward speciality; the average cost per bed day on the ward; and the financial year the costs refer to. The Information Technology or Patient Administration Departments of each centre will also be contacted, and a request submitted (via the CTRC, to maintain patient anonymity), for: Patient NHS Numbers (or some other means of linking the patient to the trial); ward name; ward speciality (if possible); start date on the ward; end date on the ward; number of occupied bed days on the ward.
- Data on Hospital Episode Statistics (HES) from the beginning of the financial year prior to baseline, to 5 years follow-up will be accessed centrally via biennial downloads from the Health and Social Care Information Centre.

Unit costs will be obtained from NHS reference costs. The number of QALY gained will be estimated by administering the EQ-5D-5L and applying a UK tariff for generating utilities.

An economic (Markov) model will be specified with appropriate health states to project lifetime costs and consequences. Costs and QALYs occurring after the first year will be discounted at 3.5% per annum. Incremental cost-effectiveness ratios will be compared with threshold values, and the joint uncertainty in costs and benefits considered (in the trial-based analysis) through the application of bootstrapping and (in the model) using probabilistic sensitivity analysis to generate cost effectiveness acceptability curves.

A separate and full Economic Analysis Plan will be developed prior to the final analysis of the trial.

8.4.2 Translational research

The Chief Investigator has an established brain tumour biobank (Walton Research Tissue Bank – WRTB; North Wales REC No 11/WNo03/2). Consent will be sought from patients for tumour tissue and serum banking, use of sample for future research projects including genetics studies, and for collaboration with academic and commercial partners. Tumour tissue (paraffin embedded and snap frozen if available) from surgery will be sent to the WRTB. Serum samples will be taken (approximately 10 mls) when the participant undergoes each MRI scan and sent to the WRTB. Future research themes will include:

1. MRI: Volumetric measurements will be used to determine tumour recurrence. The effects of radiotherapy on normal brain adjacent to the resection cavity will be studied.

2. Tumour biology: to investigate whether genetic, epigenetic or biochemical factors explain individual variation in tumour recurrence and response to radiotherapy.

3. Serum analysis: to investigate biomarkers of tumour recurrence (UK sites only).

8.5 Neurocognitive function (NCF) assessment (UK sites only)

NCF will be assessed using a standard validated battery of tests to measure verbal and visual memory, executive skills, processing speed, language, working memory, mood and visuo-spatial construction and reported on the appropriate CRF. The following tests will be used:

- Demographic questionnaire
- Hopkins Verbal Learning Test
- REY Complex Figure Test
- Dass21
- Stroop Task
- Trail Making Test
- Symbol Digit Modality Test
- WAIS-IV (Digit Span and Block Tests)
- Graded Naming Test
- Benton Verbal Fluency Test.

Consent will be sought for longer term follow up NCF assessment 5 years after surgery to assess the later effects of treatment.

8.6 Loss to Follow-up

If any of the trial participants are lost to follow-up, contact will initially be attempted through the local PI or delegated research staff at each site. Wherever possible, information on the reason for loss to follow-up will be recorded.

8.7 Trial Closure

The end of the trial is defined to be the date on which the database has been fully cleaned and frozen for the primary analysis. However, the trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (ISDMC).

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

A separate and full Statistical Analysis Plan (SAP) will be developed prior to the final analysis of the trial. The SAP will be agreed by the TSC and a copy sent to the IDSMC.

9.2 Method of Randomisation

The randomisation code list will be generated by a statistician (who is not involved with the ROAM trial) at EORTC. Following resection surgery, patients will be randomised in a 1:1 ratio between early radiotherapy and active monitoring. This ratio reflects uncertainty about which treatment arm, radiotherapy or observation, is best in terms of recurrence rate.

9.3 Outcome Measures

The primary and secondary outcomes are defined in section 4.

9.4 Sample Size

Atypical meningioma 5-year tumour recurrence rates are reported as between 39 and 58%. A 0.05 level two-sided log-rank test for equality of survival curves with 80% power would require 86 patients in each arm (total number of events required = 46) to detect an absolute reduction from 40% in the control group arm to 20%.

A strong magnitude of effect is required to impact clinical practice and establish a treatment policy across the NHS in the UK. This is due in part to the expense of radiotherapy, but also the burden to patients – due to the side effects of radiotherapy (hair loss, skin irritation, cognitive decline, secondary malignancy) and its delivery requiring patients to attend hospital daily (Monday-Friday) for 6 weeks. Patient retention will be high as patients with atypical meningioma are routinely followed up long term and data will be collected at routine clinic visits however an adjustment to allow for a 10% loss to follow up has been made, requiring a total number of 190 patients needing to be recruited.

This sample size calculation has been agreed with the EORTC. The UK arm of the trial would aim to deliver a minimum 118 patients (though there will be no limit placed on recruitment) with a total of 29 events providing 60% power. The remaining patients would be recruited across Europe within the EORTC funded collaboration.

9.5 Interim Monitoring and Analyses

9.5.1 Internal Pilot

An internal pilot will be conducted from first site initiation for 12 months. The aim of the pilot is to establish that recruitment in to the study is achievable within time frames specified. The following stop/go criteria will be used:

A) Gross total resection rate
    1) If the mean gross total resection rate is 70% or higher, proceed to the main trial.

2) If the mean gross total resection rate is between 50% and 70%, consider ways to ensure the recruitment target is still met e.g. increase the number of centres to be included. Then proceed to the main trial as amended.
3) If the mean gross total resection rate is lower than 50% and no obvious solutions exist, abandon the plan for the main trial.

B) Consent rate
1) If the consent rate is 50% or higher, proceed to the main trial.
2) If the consent rate is between 30% and 50%, consider information collected on the reasons why patients do not want to participate and identify and aspects amenable to change. Then proceed to the main trial as amended.
3) If the consent rate is less than 30% and no obvious solutions exist to increase this, abandon the plan for the main trial.

C) Loss to follow up
1) If loss to follow up occurs in no more than 10% of patients, proceed to the main trial.
2) If loss to follow up occurs in between 10% and 30% of patients then use the information captured on reasons for losses to follow up and identify any aspects amenable to change. Then proceed to the main trial as amended.
3) If loss to follow up occurs in more than 30% of patients and no obvious solutions exist, abandon the plan for the main trial.

If any of the criteria within this pilot are not met then plans on how to revise the trial will be submitted to the IDSMC and TSC prior to discussions with the trial funders. In particular, during the internal pilot screening logs at all UK sites will be kept and the information used to inform decisions on whether to amend or close. Recommendations for the continuation of the UK sites will be made incorporating experience and views of the EORTC collaboration.

9.5.2 Main trial

The trial will be monitored by an Independent Data and Safety Monitoring Committee (IDSMC) who will assess the trial data and take into account the current world-wide evidence. The IDSMC members will comply with a trial specific IDSMC charter according to International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines.

A trial statistician at CTRC will prepare the report for the IDSMC, the contents of which will be agreed by the IDSMC. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant trials, justifiy continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. The IDSMC will make recommendation to the Trial Steering Committee (TSC, see section 16) as to the continuation of the trial.

There will be an interim analysis of the primary outcome half way through the trial after approximately 50% of the total event have been observed, using Peto-Haybittle stopping rules [26]. A full statistical analysis plan will be written prior to any comparison of the treatment groups.

9.6 Analysis Plan

The trial will be analysed and reported using the 'Consolidated Standard of Reporting Trials' (CONSORT) and the International Conference on Harmonisation E9 guidelines. A full and detailed statistical analysis plan will be developed prior to the final analysis of the trial. The main features of the statistical analysis plan are included here.

The primary analysis will be by intention to treat principle as far as is practically possible. Results will be presented throughout using 95% confidence intervals and a 5% level of statistical significance. Time to event outcomes will be analysed using Kaplan Meier curves, log rank tests and Cox Proportional Hazards models. Assumptions of proportional hazards will be investigated. Ordinal categorical outcomes will be analysed using an ordinal logistic model. Continuous outcomes will be assessed using ANCOVA methods.

10 SAFETY REPORTING

10.1 Terms and Definitions

Adverse Event (AE)

Any untoward medical occurrence in a subject, including occurrences which are not necessarily caused by or related to a medicinal product or intervention.

Serious Adverse Event (SAE)

Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- Other important medical events***

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

The National Research Ethics Service defines related and unexpected SAEs as follows:

- '**related**' – that is, it resulted from any of the research procedures;
- '**unexpected**' – that is, the type of event is not listed in the protocol as an expected occurrence.

The National Research Ethics Service require that a SAE occurring to a research participant, where in the opinion of the Chief Investigator the event is *related and unexpected*, is to be reported to the main Research Ethics Committee (REC).

10.2 Notes on Adverse Event Inclusions and Exclusions

10.2.1 Include

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after administration of the intervention
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents

10.2.2 Do Not Include

- Medical or surgical procedures - the condition which leads to the procedure is the adverse event
- A hospitalisation which was planned before the patient consented for study participation and where admission did not take longer than anticipated
- Social and/or convenience admission to a hospital
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication without signs or symptoms
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

All deaths occurring after randomisation up until the end of follow-up should be reported to the EORTC **within 7 days** of the clinical research team becoming aware of the event.

10.2.3 Reporting of Pregnancy

Any pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The individual will be instructed to stop radiotherapy. All pregnancies that occur during the trial will be followed-up until conclusion/delivery and reported separately.

The PI will counsel the patient; to discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Appropriate obstetric care will be arranged.

10.3 Severity / Grading of Adverse Events

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0 (www.eortc.org\investigators-area\ctc)

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.4 Relationship to Trial Intervention

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table 2.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigator. In the case of discrepant views on causality between the investigator and local investigator, the NRES will be informed of both points of view.

Table 2: Definitions of Causality

Relationship	Description
Reasonable possibility	There is a reasonable possibility that the protocol treatment caused the event
No reasonable possibility	There is no reasonable possibility that the protocol treatment caused the event

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the SAE form and if necessary the reason for the decision will also be recorded.

10.5 Expectedness

The sponsor of the study has delegated the assessment of expectedness to the study Chief Investigator or his delegate (as identified on page 5 of this document). The expectedness assessment will be performed and compared to known complications for this type of radiotherapy.

A summary of *expected* events relating to the trial intervention as derived from relevant literature is presented in the table below.

Acute (≤3 months post radiotherapy)	Late (> 3 months after radiotherapy)
Scalp erythema	Cognitive decline
Wound breakdown	Pituitary dysfunction
Alopecia	Leucoencephalopathy
Headache	Secondary malignancy
Fatigue	
Seizures	

10.6 Follow-up After Adverse Events

All adverse events reported should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the participant to be stable.

When reporting SAEs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.7 Reporting Procedures

10.7.1 Non serious AEs

All adverse events, whether expected or not, should be reported using the trial specific adverse event CRF. Any questions concerning adverse event reporting should be directed to EORTC in the first instance.

10.7.2 Serious AEs

All SAE data must be collected on the study-specific SAE form. Please note that the SAE form is a paper form and not available in the RDC system.

SAEs should be reported within 24 hours of the local site becoming aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should assign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.
This procedure applies to all Serious Adverse Events (SAEs) occurring from the time a subject is randomised until

For radiotherapy arm:
- end of week 18

For observation arm:
- end of week 18

Any SAE that occurs outside of the SAE detection period (end of week 18), if it is considered to have a reasonable possibility to be related to the protocol treatment or study participation, has to be promptly notified.

Randomisation until end of week 18:	All SAEs
From end of week 18:	Only related SAEs

The REC will be notified of all related unexpected SAEs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. Local investigators should report any SAEs as required locally.

10.8 Responsibilities – Investigator

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to trial intervention.
All SAEs must be reported immediately by the investigator to the EORTC Pharmacovigilance Unit on an SAE form unless the SAE is specified in the protocol as not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

Minimum information required for reporting:

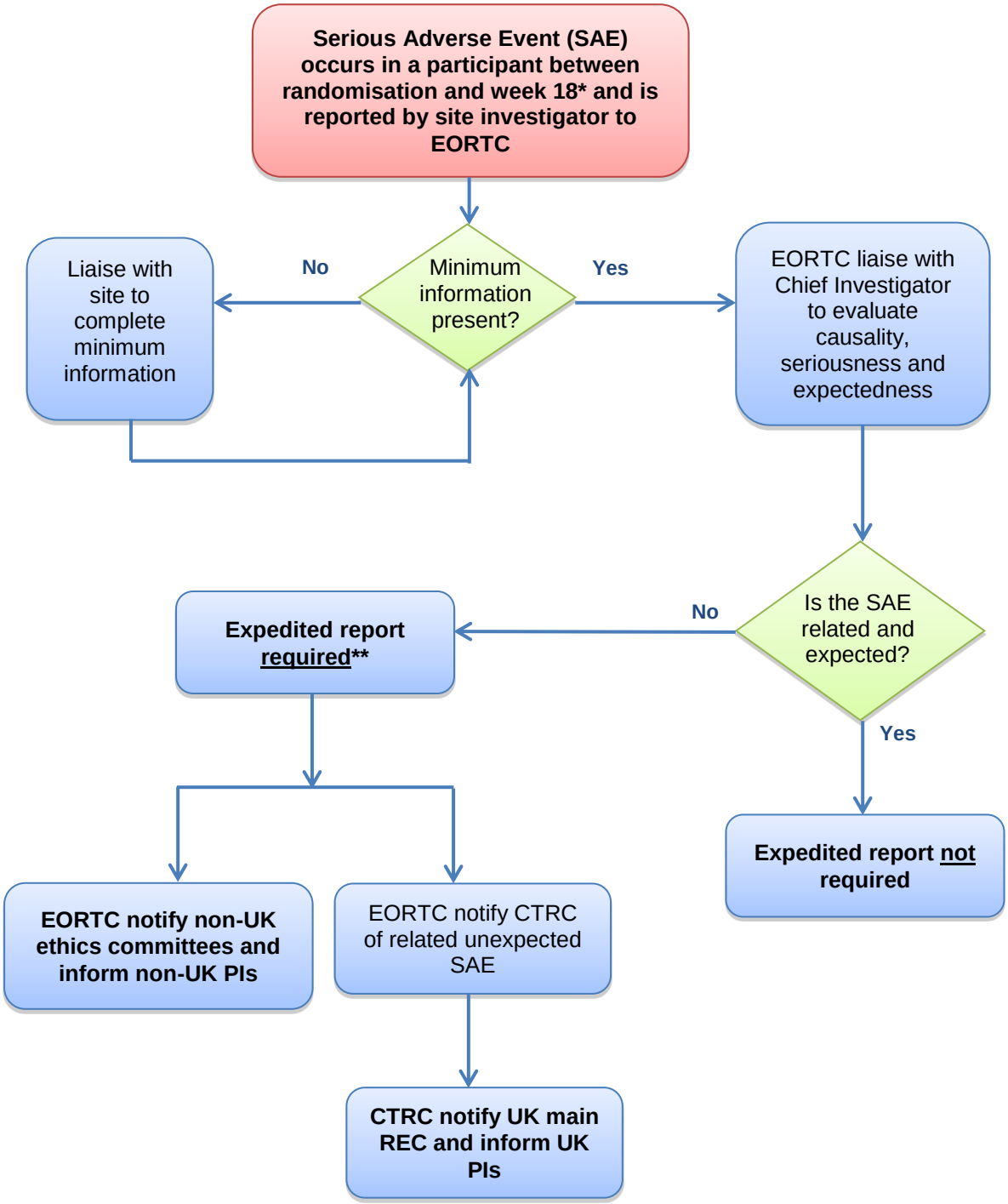
- Study identifier
- Study centre
- Patient number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

The SAE form should be completed by a designated investigator, a physician named on the 'signature list and delegation of responsibilities log' as responsible for reporting SAEs and making trial related medical decisions. The investigator should assess the SAE for the likelihood that it is a response to the trial intervention. In the absence of the designated investigator the form should be completed and signed by an alternative member of the research site trial team and submitted to the EORTC Pharmacovigilance Unit. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the EORTC Pharmacovigilance Unit. The initial report shall be followed by detailed reports as appropriate.
Send the SAE form by fax (within 24 hours) to the EORTC Pharmacovigilance Unit:

EORTC Pharmacovigilance Unit:
Fax No. +32 2 772 8027
E-mail: pharmacovigilance@eortc.be

i. The responsible investigator must **notify** their R&D department of the event (as per standard local governance procedures).
ii. In the case of an SAE the participant must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue beyond completion of protocol treatment if necessary.
iii. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the EORTC Pharmacovigilance Unit as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.
iv. The participant **must** be identified by trial number, date of birth and initials only. The participant's name **should not** be used on any correspondence.

10.9 Responsibilities – CTRC and EORTC



** If a serious adverse event occurs outside of this time window and the local investigator considers it has a reasonable possibility to be related to the protocol treatment or study participation, should also be promptly notified*
*** fatal and life-threatening RUSAEs required to be reported within 7 days of notification and non-life threatening within 15 days*

The CTRC and EORTC are undertaking duties delegated by the trial sponsor, Walton Centre NHS Foundation Trust.

The EORTC Pharmacovigilance Unit will take charge of the reporting of unexpected events to the Ethics Committees and participating investigators outside of the United Kingdom.

The CTRC will inform the MREC and participating investigators in the United Kingdom.
Both parties shall adhere to the following timelines:

- Unexpected, related SAEs which are fatal or life-threatening must be reported not later than 7 days after first becoming aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- Unexpected, related SAEs that are not fatal or life-threatening must be reported within 15 days of first becoming aware of the reaction.
- A list of all SAEs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SAEs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial and likely to affect the safety of the subjects, such as:
    a. A SAE which could be associated with the trial procedures and which could modify the conduct of the trial;
    b. A significant hazard to the subject population, such as lack of efficacy of an intervention used for the treatment of a life-threatening disease;
    c. A major safety finding from a newly completed animal study (such as carcinogenicity).
    d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same intervention in another country by the same sponsor;
    e. Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the EORTC will liaise with the Chief Investigator (or designated other personnel specified on page 5 of this document) who will evaluate all SAEs received for seriousness, expectedness and causality. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

Participant safety incidents that take place in the course of research should be reported to the NHS Commissioning Board Special Health Authority (the Board Authority) by each participating NHS Trust in accordance with local reporting procedures.

10.9.1 Safety reports

Safety reports will be generated during the course of the trial which allows for monitoring of SAEs to the trialled intervention reporting rates across sites. The EORTC will annually prepare Annual Safety Update Reports (developmental safety update report [DSUR] format) containing a list of all SAEs for submission to REC. Any concerns raised by the IDSMC or inconsistencies noted at a given site may prompt additional training at sites, with the potential for the CTRC/EORTC/TROG (as applicable) to carry out site visits if there is

suspicion of unreported AEs in participant case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines. If any safety reports identify issues that have implications for the safety of trial participants, the PIs at all institutions participating in the trial will be notified.

10.10 Contact Details and Out-of-hours Medical Cover

The current non-CTIMP (Clinical Trial of an Investigational Medicinal Product) trial is considered of low risk and a low volume of unexpected SAEs is anticipated. The trialled intervention (radiotherapy) is a well established standard practice at the participating sites and staff and personnel are highly trained to provide assistance when required. The local team will have access to the current protocol (and any future amendments) for reference and details. Medical cover will be provided by the local investigator and out-of-hours cover will be given as per routine care. If additional clinical advice and/or clarification are required the CI and named medical expert will be available.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

The trial will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996), Edinburgh (2000), Seoul (2008) and Fortaleza (2013).

This trial is a pragmatic open phase III, two-arm, multi-centre, randomised controlled trial; patients with atypical meningioma having undergone surgical resection will be enrolled in the trial. Information sheets will be provided and subsequent discussion undertaken prior to recruitment with consent. On consent they will be randomised to either the intervention (radiotherapy) or active monitoring (comparator).

Registration of UK sites will be undertaken by the CTRC at Liverpool University. Ethical approval will be sought in each participating country. Ethical approval will be overseen by the CI. The sponsor of the trial will be Walton Centre NHS Foundation Trust.

Data will be recorded through a web based system directed from the EORTC.

11.2 Ethical Approval

UK sites: The trial protocol will receive a favourable opinion of a Multi-centre Research Ethics Committee (MREC) but must undergo independent review at the R&D offices at participating sites. The local R&D office will be sent the appropriate site specific information form complete with the necessary authorisation signatures, plus any other documentation requested for review. A copy of local Research & Development (R&D) approval should be forwarded to CTRC before the site is initiated and patients recruited.

EORTC and TROG sites: The protocol must be approved by the competent authorities and/or ethics committee(s) as required by the applicable national legislation.

Consent should be obtained prior to each patient participating in the trial, after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. All patient facing material will be translated into the appropriate language for each country where participating sites are located as per standard protocol procedures. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis.

11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in CTRC coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should

adhere to Good Clinical Practice (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with experience in obtaining informed consent. This information will emphasise that participation in the trial is voluntary and that the patient may withdraw from the trial at any time and for any reason. All patients will be given opportunity to ask any questions that may arise, should have the opportunity to discuss the study with their surrogates and time to consider the information prior to agreeing to participate. A contact point where further information about the trial may be obtained will be provided.

The patient will then sign and date the informed consent document. Both the person taking consent and the patient must personally sign and date the form. A copy of the informed consent document will be given to the patient for their records. The original copy will be filed in the patient's notes and a further copy of the signed consent form will be given to the patient. One final copy of the consent form should be sent to the CTRC.

Patients will be given an adequate amount of time to consider whether to participate in the trial. The patient may, without being subject to any resulting detriment, withdraw from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

11.4 Study Discontinuation

In the event that the trial is discontinued, patients will be treated according to standard clinical care. The process for participants who withdraw early from trial treatment or from the trial completely is described in section 8.6.

12 REGULATORY APPROVAL

Regulatory approval is not required in the UK, as this is a non-CTIMP trial. EORTC and TROG will be responsible for implementing any regulatory approvals as required across their respective member states.

13 TRIAL MONITORING

Trial monitoring is carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial and that the integrity and reliability of data is verified. A risk assessment is performed for each trial coordinated by the CTRC to determine the level and type of monitoring required for specific hazards. The nature and extent of monitoring will be specific to the individual trial.

Trial Oversight Committees related to the monitoring of the trial are detailed in section 16.

13.1 Risk Assessment

In accordance with the CTRC SOP TM005 the trial risk assessment is completed in partnership between:

- Representative/s of the Trial Sponsor
- CI
- Trial Coordinator and supervising Trial Manager
- Trial Statistician and supervising Statistician
- Information Systems team
- Data Management team
- CTRC Director

In conducting this risk assessment, the contributors considered potential patient, organisational and trial hazards, the likelihood of their occurrence and resulting impact should they occur.

Monitoring of the ROAM trial will be informed by the ROAM trial specific risk assessment and will be conducted as per a detailed monitoring plan, which will describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted.

Guidance issued by the Medical Research Council, Department of Health and the MHRA on risk-adapted approaches to the management of a Clinical Trial of an Investigational Medicinal Product (CTIMP) propose a three level categorisation for the potential risk associated with the IMP, assigned according to the following categories:

Type A *'no higher than that of standard medical care';*
Type B *'somewhat higher than that of standard medical care';*
Type C *'markedly higher than that of standard medical care'.*

Although, this three level categorisation has been developed for CTIMPs the principles behind this approach have been adopted by the CTRC for assessing the risk of the intervention in non-CTIMPs.

The ROAM trial is anticipated to be categorised as ***Type A*** *'no higher than that of standard medical care'*.

13.2 Source Documents

Source data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).

Source documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).

In order to resolve possible discrepancies between information appearing in the eCRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the eCRF. The following data recorded in the eCRF should be consistent and verifiable with source data in source documents *other* than the eCRF (e.g. medical record, laboratory reports and nurses' notes).

Therefore, for data where no prior record exists and which is recorded directly in the eCRF, the eCRF will be considered the **source document**, unless otherwise indicated by the investigator. All such exemptions should be identified prior to the clinical phase of the trial. In addition to the above, date(s) of conducting informed consent, process including date of provision of patient information, randomisation number (Seqid) and the fact that the patient is participating in a clinical trial (including treatment arm) should be added to the patient's medical record chronologically, i.e. when treatment is allocated to the patient.

13.3 Data Capture Methods

Data will be collected on electronic CRFs (eCRF) with participants' data entered by participating sites. Data should be entered on to the system within 28 days of a participant visit.

13.3.1 Case Report Forms

Data will be reported on the forms specifically designed by the EORTC Headquarters for this study. Forms should be sent electronically to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture) system, with the exception of the Neurocognitive function assessment form, Quality of Life form, the SAE form and the Pregnancy notification form which are paper CRFs.

Copies of the Quality of Life forms should be sent directly to the EORTC Headquarters by one of the following means:

- By fax, to the attention of "ROG" Data manager: + 32 2 771 3810
- By scanning and e-mailing the forms (see CRF completion guidelines)
- By post to the EORTC Headquarters:

("ROG" Data Manager)

EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België – Belgique

The neurocognitive function assessment forms (UK only) should be sent directly to the trial neuropsychologist by post to:

Dr Jacqui Vinten
Clinical Psychologist
Department of Neuropsychology
The Walton Centre NHS Foundation Trust
Sid Watkins Building
Lower Lane
Liverpool
L9 7LJ

Serious Adverse Events and any pregnancies should be reported according to the procedure detailed in this protocol (see chapter on Safety Reporting).

A. Before the treatment starts:

- The patient must be randomised in the trial via the internet or in case of problems by contacting the EORTC call centre.

The electronic CRFs to be completed for a patient are available on the VISTA/RDC website one hour after the randomisation on http://rdc.eortc.be/ or on http://www.eortc.org in the section for investigators.

CRF(s) will be made available to the institution at the time the institution is authorised.

B. During/after treatment

The list of forms to be completed for this study and their submission schedule are available on the VISTA/RDC website and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

ALL forms must be electronically approved and sent by the responsible investigator or one of his/her authorised staff members with the exception of the paper quality of life form (no signature needed).

The forms must be completed electronically, with the exception of the paper forms (the Neurocognitive function assessment form, Quality of Life form, SAE form, pregnancy notification form and others if applicable), according to the schedule defined in the guidelines for completion of Case Report Forms.

The list of staff members authorised to enter data (with a sample of their signature) must be identified on the signature log and sent to the EORTC (by the responsible investigator or CTRC/TROG trial coordinator) before the start of the study. To enter the RDC system, the investigator or authorised staff member needs to use the same username and password that are used to access the interactive randomisation program (ORTA).

In all cases, it remains the responsibility of the principal investigator to check that data are entered in the database as soon as possible and that the (electronic) forms are filled out completely and correctly.

The EORTC Headquarters will perform extensive consistency checks on the received data and will issue queries in case of inconsistent data. The queries for the electronic forms will appear in the VISTA/RDC system and must be answered there directly.

For trials with paper quality of life forms: a copy of the questionnaires should be sent to EORTC Headquarters as soon as possible, while the original source document should be kept on site. If there are queries on the quality of life form, they will be raised electronically on a patient level in the VISTA/RDC system and they must be answered there directly.

For trials with several paper forms: The queries for the paper forms will be sent as a pdf file and must be printed, answered and signed by the investigator (or an authorised staff member) as soon as possible. The original form must be returned to the EORTC Headquarters and a copy must be attached to the CRF copies stored by the investigator.

The EORTC data manager will subsequently apply the corrections into the database.

When satellite institutions are involved, all contact is made exclusively with the primary institution, for purposes of data collection and all other study related issues.

If an investigator (or an authorised staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should create a request for data correction in the VISTA/RDC system.

For trials with paper quality of life forms: If an investigator (or an authorised staff member) needs to modify the paper quality of life form after the copy has been sent to the EORTC Headquarters, he/she should create a request for data correction on a patient level in the VISTA/RDC system.

For trials with several paper forms: If an investigator (or an authorised staff member) needs to modify a paper CRF after the original form has been returned to the EORTC Headquarters, he/she should notify the EORTC Headquarters by using the paper Data Correction Form. The original Data Correction Form should be sent to the EORTC Headquarters and a copy should be kept with the other CRF copies.

13.4 Clinical Site Monitoring

In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

13.4.1 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.
Case report forms will contain the patient's code and unique randomisation number (Seqid). Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

The trial team will be undertaking activities requiring the transfer of identifiable data:
Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied by recruiting centres, which requires that name data will be transferred to the trial database.

This transfer of identifiable data is disclosed in the PISC. The trial team will preserve the confidentiality of participants taking part in the study.

13.4.2 Quality Assurance and Control

Quality assurance includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. Quality control includes the operational techniques and activities done within the quality assurance system to verify that the requirements for quality of the trial-related activities are fulfilled. In accordance with the monitoring plan site visits will be conducted and source verification performed if indicated to be required as a result of central monitoring processes. To this end:

- The PI and Research Nurse from each site will attend site initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol
- The Trial Coordinator will verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended trial specific training;
- The Trial Coordinator will check safety reporting rates between sites;
- The Trial Coordinator will monitor screening, recruitment and drop-out rates between sites;
- The Data Manager will conduct data entry consistency checks and follow-up data queries;

Independent oversight of the trial will be provided by the IDSMC and independent members of the TSC, and also the final end point data adjudication committee.

13.5 Records Retention

The PI at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File until the CTRC informs the investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest).

In addition, the PI is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The PI is required to ensure the continued storage of the documents, even if the PI, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The CTRC will archive the documents in compliance with ICH-GCP guidelines, utilising the Records Management Service of the University of Liverpool. All eCRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

14 INDEMNITY

ROAM is sponsored by the Walton Centre NHS Foundation Trust and co-ordinated by the CTRC in the University of Liverpool. The Walton Centre holds insurance against claims for compensation for injury caused by participation in a clinical trial and they can offer indemnity. In terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Equivalent cover to that provided by the Clinical Negligence Scheme for Trusts should be in place for non-UK sites; this will be checked as part of the site set-up process.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

15 FINANCIAL ARRANGEMENTS

This trial is funded by NIHR Health Technology Assessment (HTA) programme. Contractual agreements will be in place between the sponsor and collaborating sites that will incorporate financial arrangements (UK sites only).

16 TRIAL COMMITTEES

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the CTRC Clinical Trials Unit and the EORTC study coordinators. The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately 4 times a year but will have more frequent and regular teleconferences in between. Refer to the TMG terms of reference and trial oversight committee membership document for further details.

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson, and independent experts in the field of neurosurgery and neuro-oncology, a biostatistician and a public/patient representative. The TSC will comprise of a minimum 75% independent members. The role of the TSC is to provide oversight for the trial, provide advice through its independent Chairman and consider recommendations from the IDSMC. The ultimate decision for the continuation of the trial lies with the TSC.

16.3 Independent Data and Safety Monitoring Committee (IDSMC)

The independent Data and Safety Monitoring Committee (IDSMC) consists of an independent chairperson, plus 2 independent members: one who is an expert in the field of neurosurgery or neuro-oncology, and one who is an expert in biostatistics.
The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in section 9.
The IDSMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the study.

17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s), Health Economist(s), EORTC Study Coordinators and Trial Manager(s). If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN and EORTC study number allocated to this trial should be attached to any publications resulting from this trial.

Funding from the NIHR HTA programme and the EORTC will be acknowledged.

The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

18 PROTOCOL AMENDMENTS

18.1 Version 3.0 (21st June 2016)

Page number	Section	Change
Throughout	Header/title page	Updated to reflect version change
1	Title page	Addition of EORTC logo
2 and 4	Signature page/Contact details	Minor change to CI job title
2	Signature page	Addition of Lead Statistician sign off.
Throughout	Page numbers	Format of page numbers changed from 'X' to '**Page** X **of Y**'
3/ Throughout	N/A	Use of 'patient' and 'participant' reviewed and amended
4	Contact details	Institution contact details removed to avoid protocol amendments if contact details change
5-7	Table of Contents	Updated to reflect changes in page numbers/heading of sections
8	Glossary	Acronyms not present in the protocol removed (e.g. CTU, IB & SPC)
Throughout	Glossary/Throughout	Replacement of 'RTQA' with 'RTTQA'
9/ Throughout	Protocol summary (Inclusion Criteria)/ Throughout	References to 2007 WHO criteria updated to reflect the recent 2016 WHO criteria
9/ Throughout	Protocol summary (Exclusion Criteria)/ Throughout	Exclusion criteria 'Previous radiotherapy to the brain or meninges interfering with the protocol treatment plan' removed and replaced with '*Radiation-induced meningioma*'
9/ Throughout	Protocol summary (Exclusion Criteria)/ Throughout	Exclusion criteria 'Clinical evidence of second malignancies, except a history of cervix carcinoma in situ and/or basal cell carcinoma' amended to '*Clinical evidence of second malignancy, except for cervix carcinoma in situ or basal cell carcinoma, and history of invasive malignancy unless treated with curative intent and the patient has not been disease free for the last five years*'
10	Protocol summary (Study Centres and Distribution)	Text amended to state that ROAM will be an International multicentre European study
10/ Throughout	Protocol summary (Study Centres and Distribution)/ Throughout	References to Trans Tasman Radiation Oncology Group (TROG) and European Organisation for Research and Treatment of Cancer (EORTC) added where applicable
10/ Throughout	Protocol summary (Study Duration)/ Throughout	Clarification that there will be no limit on the number of patients to be recruited from UK, EORTC or TROG sites within the overall trial target
10	Protocol summary (Description of Agent/Intervention – Stage 1)	Clarification that the qualitative study embedded within stage 1 of ROAM will be in UK sites only
10/ Throughout	Protocol summary (Primary Objective)/ Throughout	Primary objective amended to include death due to any cause: 'To determine whether early adjuvant fractionated radiotherapy reduces the risk of tumour recurrence *or death due to any cause* compared to active monitoring in newly diagnosed atypical meningioma'
12/ Throughout	Schematic of study design/Throughout	Clarification that certain assessments are applicable for UK sites only and time points defined
15	2.4.1	Addition of '*In the very rare instance that a patient experiences loss of capacity during radiotherapy, it will be at the clinicians' discretion to treat the cause of this and, if thought to be in the patients' best interest, continue with radiotherapy*.'

16	3	Minor clarification of requirements for initiating UK, EORTC and TROG sites
16	3.1	Clarification that centre inclusion criteria 'b' is applicable to UK sites only
17	4.2	'Toxicity of radiotherapy' amended to include CTCAE: *'Toxicity of radiotherapy assessed by CTCAE (Common Terminology Criteria for Adverse Events)'*
17	4.2	Definitions of Disease free survival and Overall survival added (moved from section 9.3)
18-19	5.3.1	Text amended to clarify process of notifying CTRC/EORTC/TROG of patient transfers
21	6.2.1.2	Change to the way in which audio-recordings will be transferred and uploaded for the qualitative study
21-22	6.2.1.3	Clarification on which details will be captured on the qualitative study pro forma and how these are to be returned
23-24	6.3	Section on randomisation updated and clarifications made to reflect EORTC processes
24	6.4	Addition of *'It is accepted that some patients may have already undergone an early post-operative MRI scan (i.e. within 72 hours), however the MRI should still be performed at 6 weeks after surgery.'*
24	6.4	Text amended to *'Patient performance status and symptom-directed physical and neurological examination will be recorded.'*
24	7.1	Clarification that appendix 2 will be for all sites.
24/ Throughout	7.1/Throughout	Full name of EQ-5D given as *EQ-5D-5L*
25-27	7.2	Changes to text and ordering of paragraphs/sections throughout the Arm A: Radiotherapy section.
25	7.2.1	Text amended to reflect that '*radiotherapy will be planned and delivered with modern techniques, including but not limited to IMRT and volumetric modulated arc therapy'* (i.e. IMRT not mandatory).
25	7.2.2	Section added detailing patient immobilisation during the administration of radiotherapy
25-26	7.2.3	Data acquisition & Definitions of Target Volumes & Organs at Risk sections combined
26	7.2.4	Reference to *'or similar modern technique'* added when referring to IMRT and reference to *'table 1'* removed
26-27	7.2.5.4	Prescribed dose of radiotherapy and fractionation clarified
27	7.2.6	References to dose limits removed
27	7.2.6, Table 1	Table illustrating organ structures and optimal/mandatory radiotherapy fractions has been removed
27	7.2.9	Brief description of RTTQA programme added
27	7.3	Clarification that participants in Arm B will not receive radiotherapy but will be followed-up as participants in Arm A
29/ Throughout	8.1/ Throughout	'Seqid' added to clarify this as an alternative term for randomisation number.
30	Table 1 (Trial plan)	The following changes have been made: • Table 2 renumbered as Table 1 • Time points defined for semi-structured interviews, baseline assessments & start of treatment • Visit window changed for consent • Visit windows added for semi-structured interview, baseline assessments & start of treatment • Assessment of AEs moved further up the table • Neurocognitive function assessments grouped together • Tumour tissue and serum sample time points separated out

		• Serum sample time point added at baseline MRI (omitted in error) • Resource use questionnaire time points added at baseline QoL & at 6 months after surgery (omitted in error)
31-32	8.4.1	Clarification added that *'trial nurses will complete the questionnaires with patients during follow up visits'*
32	8.4.2	Clarification that the CI has an established biobank
32	8.5	All names of neurocognitive function assessments listed
33	8.7	Minor changes to wording around end of trial definition in respect of database being fully cleaned and frozen for the primary analysis
34	9.2	Change in text to state EORTC will generate randomisation code list and not CTRC
34	9.3	Definition of DFS and OS removed and guidance added to state that outcomes are defined in section 4
34-35	9.5.1	Details of *'Internal Pilot'* added (omitted in error)
35	9.5.2	'Main trial' heading added
36	9.6	References to cumulative incidence and competing risks removed
37	10.1	Examples of 'other important medical events' added
38	10.2.2	Confirmation that planned hospitalisation and convenience admissions are not be included as AEs
38/ Throughout	10.2.2/Throughout	Clarification that (S)AE management and some reporting will be carried out by EORTC, not CTRC
38	10.2.3	Details added to pregnancy reporting process and timelines
38-39	10.3	Clarification that severity of all AEs should be graded using CTCAE v4.0
39	10.4	*Definitions of Causality* table updated and information of alternative causes added.
39	10.5	Information about who will assess expectedness added and summary of expected events updated.
40	10.7	Reporting procedures clarified and the following changes were made: • Clarification that questions concerning AE reporting should be directed to EORTC in the first instance • Clarification that all AEs, whether expected or not, should be reported • Clarification that SAE form is paper-based • Clarification that SAE reporting for both arms of the trial occurs from randomisation to end of week 18 • Clarification that SAEs outside detection period should be notified in considered to be related to treatment/trial • Clarification of which SAEs are to be reported until end of week 18 and after the end of week 18 • Details of timelines for reporting SAEs to REC (S)AE reporting schematic removed
41	10.8	The following changes were made: • Clarification that SAEs are to be reported to EORTC Pharmacovigilance Unit within 24 hours Details of EORTC Pharmacovigilance Unit added
42-44	10.9	The following changes were made: • Schematic added to clarify CTRC & EORTC responsibilities • Details added of CTRC & EORTC responsibilities and reports to be prepared Clarification that safety incidents should be reported to NHS Commissioning Board Special Health Authority (the Board Authority) and not the National Patient Safety Agency

49	13.2	The following changes were made: • Reference to patients registration number removed (reference to randomisation number only) Clarification that treatment arm should be added to patient's medical record
49-51	13.3	The following changes were made: • Addition of Neurocognitive Function assessment form & pregnancy notification form to the list of paper CRFs • Addition of 'ROG' to Data Manager title • Addition of lead neuropsychologist contact details • Clarification that patients can be randomised by contacting EORTC call centre if there are problems randomising online • Reference to 'registration number' removed Clarification that EORTC signature log can be sent to EORTC by PI or CTRC trial coordinator
51	13.4.1	'Patient's initials' replaced with 'patient's code'
54	15	Clarification that funding secured through NIHR HA programme is in respect to UK sites only
55	16.1	Text added to state that the TMG will include EORTC Study Coordinators
55	16.3	Text 'name and area of expertise' deleted (added in error)
56	17	The following changes were made: • Health Economists and EORTC Study Coordinators added to the list of named authors for publication purposes • Clarification that EORTC study number will be added to publications and EORTC funding will be acknowledged
57	18.1	Table updated, summarising the amendments made to the previous version of the protocol (Version 2.0 18th March 2016).

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20 APPENDICES

Appendix 1: Performance status evaluation

WHO PERFORMANCE STATUS

Score	Definition
0	Asymptomatic and fully active
1	Symptomatic; fully ambulatory; restricted physically strenuous activity
2	Symptomatic; ambulatory; capable of self-care; more than 50 percent of waking hours are spent out of bed
3	Symptomatic; capable of limited self-care; spends more than 50 percent of time in bed but not bedridden
4	Completely disabled; no self-care; bedridden

Appendix 2: Quality of Life Assessments

Content only described below (formatting on case report forms is different and is approved by the EORTC).

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Not at All (1), A little (2) Quite a Bit (3) Very Much (4)

1 Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? 1 2 3 4

2 Do you have any trouble taking a long walk? 1 2 3 4

3 Do you have any trouble taking a shortwalk outside of the house? 1 2 3 4

4 Do you need to stay in bed or a chair during the day? 1 2 3 4

5 Do you need help with eating, dressing, washing yourself or using the toilet? 1 2 3 4

During the past week: Not at All (1), A little (2) Quite a Bit (3) Very Much (4)

6. Were you limited in doing either your work or other daily activities? 1 2 3 4

7. Were you limited in pursuing your hobbies or other leisure time activities? 1 2 3 4

8. Were you short of breath? 1 2 3 4

9. Have you had pain? 1 2 3 4

10. Did you need to rest? 1 2 3 4

11. Have you had trouble sleeping? 1 2 3 4

12. Have you felt weak? 1 2 3 4

13. Have you lacked appetite? 1 2 3 4

14. Have you felt nauseated? 1 2 3 4

15. Have you vomited? 1 2 3 4

16. Have you been constipated? 1 2 3 4

During the past week: Not at All (1), A little (2) Quite a Bit (3) Very Much (4)

17. Have you had diarrhoea? 1 2 3 4

18. Were you tired? 1 2 3 4

19. Did pain interfere with your daily activities? 1 2 3 4

20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? 1 2 3 4

21. Did you feel tense? 1 2 3 4

22. Did you worry? 1 2 3 4

23. Did you feel irritable? 1 2 3 4

24. Did you feel depressed? 1 2 3 4

25. Have you had difficulty remembering things? 1 2 3 4

26. Has your physical condition or medical treatment interfered with your family life? 1 2 3 4

27. Has your physical condition or medical treatment interfered with your social activities? 1 2 3 4

28. Has your physical condition or medical treatment caused you financial difficulties? 1 2 3 4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall healthduring the past week? 1 2 3 4 5 6 7 (Very poor- Excellent)

30. How would you rate your overall quality of life during the past week? 1 2 3 4 5 6 (Very poor- Excellent)

EORTC QLQ -BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week: Not at All (1), A little (2) Quite a Bit (3) Very Much (4)

31. Did you feel uncertain about the future? 1 2 3 4
32. Did you feel you had setbacks in your condition? 1 2 3 4
33. Were you concerned about disruption of family life? 1 2 3 4
34. Did you have headaches? 1 2 3 4
35. Did your outlook on the future worsen? 1 2 3 4
36. Did you have double vision? 1 2 3 4
37. Was your vision blurred? 1 2 3 4
38. Did you have difficulty reading because of your vision? 1 2 3 4
39. Did you have seizures? 1 2 3 4
40. Did you have weakness on one side of your body? 1 2 3 4
41. Did you have trouble finding the right words to express yourself? 1 2 3 4
42. Did you have difficulty speaking? 1 2 3 4
43. Did you have trouble communicating your thoughts? 1 2 3 4
44. Did you feel drowsy during the daytime? 1 2 3 4
45. Did you have trouble with your coordination? 1 2 3 4
46. Did hair loss bother you? 1 2 3 4
47. Did itching of your skin bother you? 1 2 3 4
48. Did you have weakness of both legs? 1 2 3 4
49. Did you feel unsteady on your feet? 1 2 3 4
50. Did you have trouble controlling your bladder? 1 2 3 4