Supplementary 1 - Radiotherapy Treatment Details

Initial radiotherapy dose and schedule

The radiotherapy treatment is standard of care and consists of a conventionally fractionated regimen delivering either:

1. A total dose of 60Gy, in a once daily schedule of 2 Gy per fraction for a total of 30 fractions, completed optimally in 6 weeks but up to a maximum of 7 weeks (recommended for good performance status participants aged 65 years and under); or

2. A total dose of 40.05 Gy, in a once daily schedule of 2.67 Gy per fraction for a total of 15 fractions, completed optimally in 3 weeks but up to a maximum of 4 weeks (recommended for participants aged ≥65 years or those of ECOG performance status 2 who are nevertheless judged appropriate for treatment).

Treatment should ideally start within 4-6 weeks after surgery (maximum 7 weeks + 3 days).

A single phase treatment volume will be used. At the treating Radiation Oncologist's discretion, coverage of the volume may be compromised when there is overlap with a critical normal structure (e.g. brainstem, optic nerves and chiasm).

Gross Tumour Volume (GTV)

Target volume definition should be based on magnetic resonance imaging (MRI). Image fusion (= co-registration) of the MRI scans and the planning CT scan must be used for target volume definition. The accuracy of image co-registration should remain within ≤ 0.3cm. An exception to these requirements is where a patient has a medical contraindication to MRI, whereby CT-based planning can be undertaken instead.

The GTV is the volume encompassed by the surgical cavity and any enhancing tissue as defined on the post-operative T1 gadolinium-enhanced MRI sequence. In the setting of a limited resection or biopsy, the pre-operative T1 gadolinium-enhanced MRI sequence can be used.

Abnormal T2 FLAIR signal on post-operative MRI that is suspicious for gross non-enhancing tumour rather than tumour or surgery related oedema should be considered (at the discretion of the radiation oncologist) for inclusion within the GTV.

Clinical Target Volume (CTV)

The Clinical Target Volume (CTV) is defined by a 1.5 cm volumetric expansion of the GTV. The CTV extends to the contralateral hemisphere only when midline structures such as the corpus callosum and the contralateral hemisphere are invaded by tumour. The tentorium and meninges should be considered as anatomical borders and therefore a margin of 0-0.5cm is

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sufficient to encompass the microscopic spread at these borders. Volumetric expansion may also be reduced in areas adjacent to sensitive structures.

Planning Target Volume (PTV)

The Planning Target Volume (PTV) will take into account uncertainties of planning and setup. This margin should be based upon known departmental values, but will usually be in the order of 0.3 cm. All margins should be added using a three-dimensional (3-D) growth algorithm where possible.

Planning procedure

Patient is positioned either supine or prone depending on site of lesion, in an immobilisation device (any fixation system with relocation accuracy < 0.5 cm).
The use of CT-based planning is mandatory. A maximum CT slice thickness of 0.3 cm is recommended. Co-registration of CT and MRI data is mandatory.
Use of shielding blocks or a multi-leaf collimator is mandatory. Planning should conform to ICRU 50/62/83 criteria for target volume coverage, dose normalization and homogeneity [31].

Instructions for treatment delays and dose modifications for adverse events (AEs) are specified below. In general, treatment should be withheld during adverse events of severity Grade 3-4 (according to the Common Terminology Criteria for Adverse Events (CTCAE)), at the investigator's discretion.

Radiotherapy Treatment technique

Treatment must be delivered with a linear accelerator with a minimum nominal beam energy of 4-6 MV. The volume should be treated by multiple field technique, all fields treated at each fraction.

The use of a vertex field is optional. If used it requires either a diagram or photograph of treatment position. Treatment position verification is carried out by at least weekly portal imaging or portal films according to the institution's standards.

- For 3DCRT: The prescription dose is specified and reported at the ICRU reference point as defined in ICRU Reports #50, #62 and #83[31-33].
- For Intensity-modulated RT (IMRT): Treatment with IMRT is allowed provided that conventional fractionation and dose prescription according to ICRU #50, #62 and #83 is used. No simultaneous integrated boost is allowed. IMRT will be allowed providing sites can provide quality assurance procedure information. Tomotherapy and VMAT techniques will all be considered IMRT for purposes of this trial.

*Stereotactic radiotherapy, implants, brachytherapy are **NOT ALLOWED***.

Dose prescription, fractionation

Dose prescription and recording will be according to ICRU 62-criteria. Dose homogeneity requirements in the PTV shall be -5% + 7%. The PTV should be encompassed by the 95% isodose. The 90% isodose is acceptable in close proximity to organs-at-risk.
Either:

1. Total dose: 60Gy; dose per fraction: 2Gy in 30 daily fractions
2. Total dose: 40.05Gy; dose per fraction: 2.67Gy in 15 daily fractions

Dose limitation to critical structures

If delivering a total dose of 60Gy:
Organs-at-risk to be spared if possible are: eyes, optic chiasm, optic nerves, brainstem, ear, uninvolved brain areas. The optic chiasm, optic nerves and brainstem (= medulla, pons and midbrain) should **ideally** not receive doses higher than **56**Gy. The eye balls including the lens and retina should not be included in any direct beam. Maximum dose for the lens: < 6Gy, for the retina: ≤ 36Gy. Maximum dose for the eye: 45Gy.

If delivering a total dose of 40.05Gy:
Organs-at-risk to be spared if possible are: eyes, optic chiasm, optic nerves, brainstem, ear, uninvolved brain areas. The optic chiasm, optic nerves and brainstem (= medulla, pons and midbrain) should **ideally** not receive doses higher than **40**Gy. The eyeballs including the lens and retina should not be included in any direct beam. Maximum dose for the lens: < 6Gy, for the retina: ≤ 30Gy. Maximum dose for the eye: 30Gy.

RT dose interruptions and reductions

No dose adjustments are recommended irrespective of length of treatment interruptions. Maximum overall radiotherapy treatment time is 7 weeks.

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Supplementary file 3 – MRI protocol

The FIG trial MRI protocol is in accordance with the consensus recommendations for a dynamic susceptibility contrast MRI protocol for use in high grade gliomas [34].

Image Acquisition

The following image sequences are required at each MRI acquisition:

- 3D T1 Gradient-recalled echo (acquired in axial or sagittal plane, with or without fat saturation)
- 3D FLAIR (acquired in axial or sagittal plane)
- Ax 2D DWI
    - DCE perfusion acquisition with 1+1 dosage is full dose of 0.1 mmol/kg + full dose if 0.1 mmol/kg or the equivalent of other gadolinium contrast agents are used.
    - Alternate MRI contrast agents to Dotarem may be used, by administering the full dose acquisition preload before DSC and DCE. Sites must ensure the same contrast agent is being used for both baseline and follow-up MRI scans as per imaging protocol.
- 5 minutes after this injection, second injection with same dose; DSC perfusion with further 0.1 mmol/kg (2 min after DCE perfusion)
- Ax T2
- Vol T1 C+ (identical sequence to pre-contrast)

Notes and detailed imaging parameters are specified below. In addition, the following are optional at the discretion of the site:

- SWI
- 3D DIR

Additional sequences may be performed to meet the site's standard of practice.

Image Acquisition Notes

- Field strength 3T only.
- The same scanning equipment, technique, and parameters used at baseline should be used for all subsequent assessments for that participant whenever possible (sites with 2 identical machines can use either for follow up).
- Perfusion acquisitions should use 3-5 mm slice thickness, 3 mm preferred, with in plane resolution of ~2.5x2.5 mm or better. For the DCE it is hoped that the systems will have modern accelerated T1 FLASH sequences that will allow temporal resolutions between 1 and 2 seconds. A fast T1 Mapping sequence (<2mins) with the same image resolutions will be required for the DCE post processing.
- 3D T1 sequence used for pre and post contrast should be identical.
- Fat saturation is optional but same option used for initial study should be used on follow up studies for each participant.

- The same contrast agent used for a participant's baseline study should be used for all follow up studies for that participant.
- The volume acquisitions should be reformatted parallel and perpendicular to plane of axial scans.
- Axial post-contrast reformatted images should have same slice position, thickness and gap as perfusion images to facilitate correlating post contrast and perfusion images.

▪ Image Acquisition Parameters

	3D T1w Pre	Ax 3D FLAIR [i]	Ax 2D DWI	DCE Contrast Injection [a]	DCE Perfusion [j]	DSC Contrast Injection [a]	DSC Perfusion [h]	Ax 2D T2w	3D T1w Post [b]
Sequence	IR-GRE[d,e]	TSE[c]	EPI[f]		TWIST/TRICKS/TRAK		GE-EPI	TSE[c]	IR-GRE[d,e]
Plane	Sagittal/Axial	Sagittal/Axial	Axial		AXIAL		Axial	Axial	Axial / Sagittal
Mode	3D	3D	2D		3D		2D	2D	3D
TR [ms]	2100[g]	>6000	>5000		1000-2000		1500	>2500	2100[g]
TE [ms]	Min	90-140	Min		Min		25-35	80-120	Min
TI [ms]	1100[h]	2000							1100[h]
Flip Angle	10º-15º	90º/≥160º	90º/180º		20-30		60º	90º/≥160º	10º-15º
Frequency	256	≥256	128		128		128	256	256
Phase	256	≥256	128		128		128	256	256
NEX	≥1	≥1	≥1		>120 Reps Inject after 20 seconds of baseline		>120 Reps; Inject after 45s of baseline data (>30 time points)	≥1	≥1
FOV (whole brain)	256mm	<250mm	240mm		240		240mm	240mm	256mm
Slice Thickness	1mm	3mm	3mm		3		3mm	3mm	1mm
Gap/Spacing	0	0	0		0		0-5mm	0	0
Options/Notes			*b* = 0, 500, and 1000 s/mm^2 ≥3 directions		Acquire same data with 5 different flip angles 5,10,20,30,60 before baseline imaging and contrast injection		Cover tumor; 18-20 Ga IV, right arm; 3-5 mL/sec inj. rate		
Parallel Imaging	Up to 2x	Up to 2x	Up to 2x		Up to 2x		Up to 2x	Up to 2x	Up to 2x
Scan Time (Approx)	5-8 min	5-8 min	3-5 min		3-4 Min		3 min	7 min	5-8 min

Supplementary file 4 – FET-PET and FDG-PET imaging

FET Administration, Image Acquisition and Reconstruction

- FET dose is 200 MBq +/- 10%.
- Head holders to be used (where available and practical).
- The administration of FET will be performed on the PET camera as a dynamic acquisition.
- Administration of FET is by slow IV injection over 20-30 seconds, followed by a minimum of 20mL saline flush.
- CT head first followed by list mode acquisition for 40 minutes commencing at the start of the slow injection over 20-30 seconds of FET.
- Ensure image acquisition commences immediately after FET is administered.
- Two reconstructions are required:
    - Site -specific protocol for reconstruction, zoom, matrix size, attenuation correction and post reconstruction filters should be performed, with the specifications listed in the site study folder.
    - A "harmonised" protocol, where no post reconstruction filters and no point-spread-function is applied.
- For each reconstruction, rebin list mode to give:
    (a) DYNAMIC: a dynamic study of 40 frames of 1 minute each;
    (b) STATIC 1: a single static image from 21-30 minutes; and
    (c) STATIC 2: a single static image from 21-40 minutes.

FDG Administration, Image Acquisition and Reconstruction

- FDG dose is 185MBq +/- 10%.
- Administration of FDG is by slow IV injection over 20-30 seconds, followed by a minimum of 20mL saline flush.
- Uptake phase is 60mins, during which time the patient rests in a quiet, low stimulus environment
- CT head first followed by list mode acquisition for 10 minutes commencing 60 minutes after injection.
- Two reconstructions are required:
    - Site specific protocol for reconstruction, zoom, matrix size, attenuation correction and post reconstruction filters should be performed, with the specifications listed in the site study folder.
    - A "harmonised" protocol, where no post reconstruction filters and no point-spread-function is applied.
- For each reconstruction, rebin list mode to give a single static image.

Data Collection

The following parameters will be requested from each of the sites at study establishment, and should remain for each of the PET imaging studies:

- Reconstruction algorithm (e.g. iterative)
- Free reconstruction parameters (number of subsets and number of iterations).
- Zoom.
- Matrix size.
- Attenuation correction plus scatter correction plus resolution recovery plus time-of-flight if available should be used.
- Identification of any post-reconstruction filter (e.g., 5mm FWHM Gaussian).
- Images (FET DYNAMIC, STATIC 1 and STATIC 2, and FDG-PET, for both reconstruction methods) will be submitted to TROG QA, together with a form indicating any deviations from protocol including from the above parameters.

QA Requirements

- PET-CT scanners and PET-MR scanners for the trial require ARTnet certification.
- The same scanner should be used for all PET imaging studies.
- All PET scans should be reviewed by a Nuclear Medicine specialist immediately following acquisition and reconstruction in order to confirm image integrity, completeness and quality.

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Supplementary file 5 – Scan Interpretation: FET1 and Radiotherapy Planning

Scan Interpretation: FET1 and Radiotherapy Planning

The local site Nuclear Medicine specialist will delineate the FET-PET gross tumour volume ("NM_GTV_PT1MR1") on FET1 using the MIM software FIG trial Workflow. Each site will be provided with the FIG trial MIM Workflow. The Workflow provides automated step by step guidance to complete the below activities. The FET-PET tumour volume is then transferred to the site Radiation Oncologist for generation of new GTV/CTV/PTV.

The following protocol should be followed, using the MIM FIG trial Workflow (note: this protocol requires using the site-specific reconstruction, and many of these steps will be automated by the MIM Workflow):

1. Use STATIC 2 (21-40min) FET-PET scan for analysis at timepoint FET 1;
2. Fuse the planning MRI to the Static FET2 images (see Section 6.4).
3. Define normal region by drawing a crescent-shaped volume-of-interest on grey/white matter of contralateral hemisphere and obtain SUVmean. The Workflow will automatically save the delineated region structure as "Background".
4. Calculate threshold value by 1.6 x SUVmean.
5. Draw a region around the tumour and apply the threshold value to generate the Static_GTV_Final volume of interest.
6. Review region and modify if appropriate, comparing the volume against the fused MRI and removing areas of cavity and/or scalp.
7. Complete the free-text section of the FET1 Worksheet, describing any reasons for modifying the region from the 1.6 x SUVmean.
8. Save the fused tumour VOI/MRI/FET 1 dataset (i.e., incorporating all Workflow generated regions of interest, including the Static_GTV_Final structure set files). Clone (copy) the Static_GTV_Final structure and rename to '**NM_GTV_PT1MR1'** and save. The fused datasets and the structure set should then be transferred to Radiation Oncology after completion of the participant's chemo-radiotherapy (or at least 4weeks post radiation therapy commencement). A proportion of cases with hybrid volumes will also undergo central review.
9. Complete the FET1 Worksheet.
10. In the radiotherapy planning system, the Radiation Oncologist should copy NM_GTV_PT1MR1 to a new structure, RO_GTV_PT1MR1, and make any adjustments they feel necessary (according to adjacent critical structures etc). **This step should be performed without reference to the original target volumes.** In some cases, no changes may be required. ***Note: the NM_GTV_PT1MR1 may not be a contiguous closed region of interest.***
11. The Radiation Oncologist should then create a CTV based on RO_GTV_PT1MR1 o RO_CTV_PT1MR1 = (RO_GTV_PT1MR1) + 1-1.5cm Margin

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Supplementary file 6 - Scan Interpretation: FET3 Clinical Assessment for Tumour Recurrence

As for each FET-PET timepoint, the FIG trial MIM Workflow is used for FET image interpretation.

Order of site and central PET review

1. FET3 review (reviewer blinded to FET2 results and blinded to FDG PET)
2. FET3 review in conjunction with FET2
3. FET3 review in conjunction with FDG-PET (if available)*

* Standard clinical FDG-PET scan and review should occur prior to FET3 imaging review.
Note: The reporting Nuclear Medicine physician must remain blinded to the FET 3 results.

FET3 is performed at the time of suspected tumour recurrence. In addition to providing a clinical report, the site's Nuclear Medicine Physician will provide an interpretation of the scan for disease progression, via the trial case report form (CRF). This interpretation and the acquired images will be uploaded for central review to TROG to assess for concordance. Site and then central review are to be performed within 7 calendar days of image acquisition.

Visual and semi-quantitative assessment of the FET3 scan will be performed.

The following semi-quantitative parameters will be recorded in the FET3 Worksheet:

- Tumour: SUVmax, SUVmean, Volume, Total activity (TLG), TBRmean, TBRmax
- Background: SUVmean
- Dynamic: TAC type (I, II or III) and TTP

Based on visual and semi-quantitative assessment the local reporting NM Physician will allocate one of the following categories for interpretation of the scan:

1) No significant abnormal FET-PET activity: normal scan
2) Treatment predominant changes / pseudoprogression
3) Equivocal
4) Probable tumour
5) Highly likely tumour recurrence / progression
6) New lesion

Based on these categories, the final clinical report issued to the referring clinician will state one of the following conclusions:

- Scan consistent with treatment predominant changes (categories 1 and 2)
- Scan findings are equivocal (category 3)
- Scan findings are consistent with tumour progression (categories 4, 5 and 6)

The MRI scans will be available to assist in image interpretation.