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[18F]-fluoroethyl-L-tyrosine (FET) in glioblastoma (FIG) TROG 18.06 study: protocol for a prospective, multicentre PET/CT trial

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ABSTRACT

Introduction Glioblastoma is the most common aggressive primary central nervous system cancer in adults characterised by uniformly poor survival. Despite maximal safe resection and postoperative radiotherapy with concurrent and adjuvant temozolomide-based chemotherapy, tumours inevitably recur. Imaging with O-(2-[18F]-fluoroethyl)-L-tyrosine (FET) positron emission tomography (PET) has the potential to impact adjuvant radiotherapy (RT) planning, distinguish between treatment-induced pseudoprogression versus tumour progression as well as prognostication.

Methods and analysis The FET-PET in Glioblastoma (FIG) study is a prospective, multicentre, non-randomised, phase II study across 10 Australian sites and will enrol up to 210 adults aged ≥18 years with newly diagnosed glioblastoma. FET-PET will be performed at up to three time points: (1) following initial surgery and prior to commencement of chemoradiation (FET-PET1); (2) 4 weeks following concurrent chemoradiation (FET-PET2); and (3) within 14 days of suspected clinical and/or radiological progression on MRI (performed at the time of clinical suspicion of tumour recurrence) (FET-PET3). The co-primary outcomes are: (1) to investigate how FET-PET versus standard MRI impacts RT volume delineation and (2) to determine the accuracy and management impact of FET-PET in distinguishing pseudoprogression from true tumour progression. The secondary outcomes are: (1) to investigate the relationships between FET-PET parameters (including dynamic uptake, tumour to background ratio, metabolic tumour volume) and progression-free survival and overall survival; (2) to assess the change in blood and tissue biomarkers determined by serum assay when comparing FET-PET data acquired prior to chemoradiation with other prognostic markers, looking at the relationships of FET-PET versus MRI-determined site/s of progressive disease post chemotherapy treatment with MRI and FET-PET imaging; and (3) to estimate the health economic impact of incorporating FET-PET into glioblastoma management and in the assessment of post-treatment pseudoprogression or recurrence/true progression. Exploratory outcomes include the correlation of multimodal imaging, blood and tumour biomarker analyses with patterns of failure and survival.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Largest multicentre prospective study addressing the impact of O-(2-[18F]-fluoroethyl)-L-tyrosine (FET) positron emission tomography (PET) in the management of glioblastoma, including adjuvant radiation planning, differentiating pseudoprogression from recurrent and/or progressive disease, the role of FET-PET in prognostication, as well as a robust health economic analysis.
⇒ Development and implementation of robust multisite national credentialling and on-trial quality assurance programmes addressing both nuclear medicine and radiation oncology delivery.
⇒ Development of integrated FET-PET and MRI-specific criteria for assessment of treatment response in the management of study participants with newly diagnosed glioblastoma.
⇒ A limitation of the study includes varying levels of site experience with FET-PET interpretation and reporting, although this is addressed via a robust trial credentialling programme assessing both technical capability and upskilling of nuclear medicine specialist and radiation oncologist expertise. Ongoing quality assurance in the prospective phase of the trial will also serve to reduce interobserver variability.

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Ethics and dissemination The study protocol V.2.0 dated 20 November 2020 has been approved by a lead Human Research Ethics Committee (Austin Health, Victoria). Other clinical sites will provide oversight through local governance processes, including obtaining informed consent from suitable participants. The study will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Results of the FIG study (TROG 18.06) will be disseminated via relevant scientific and consumer forums and peer-reviewed publications.

Trial registration number ANZCTR ACTRN12619001735145

INTRODUCTION

Background and rationale

Glioblastoma multiforme (GBM) is the most common primary brain cancer in adults[1] with poor survival outcomes resulting in a median survival of 15 months and a 5-year survival of less than 5%.[2] Since the introduction of concurrent temozolomide (TMZ) chemotherapy with postsurgical radiation in 2005, there has been little progress in improving outcomes.[2 3] There remains a pressing need for the incorporation of accurate and timely imaging as a cornerstone in optimal management,[4] prognostication and effective decision-making to help improve the current dismal outcomes in adult glioblastoma.

Amino acid (AA) positron emission tomography (PET) imaging tracers (such as O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET-PET)) has been shown to be accurate in detecting the site and extent of GBM in both initial diagnostic and recurrent disease settings. Figure 1 demonstrates imaging from serial FET-PET scans including baseline, retest (1 week) and post-therapy (see figure 1),[5] although studies to date have been almost exclusively single-centre with relatively small sample sizes.[6–8] The utility of AA FET-PET imaging tracers is based on the observation that AA transport, primarily mediated by the L-Type AA transporter, is increased in malignant transformation independent of a disrupted blood-brain barrier (BBB) and is also present in non-enhancing tumour sites, therefore yielding a high tumour to normal tissue contrast and potentially allowing more sensitive detection of tumour in non-gadolinium contrast enhancing areas.[4 9 10]

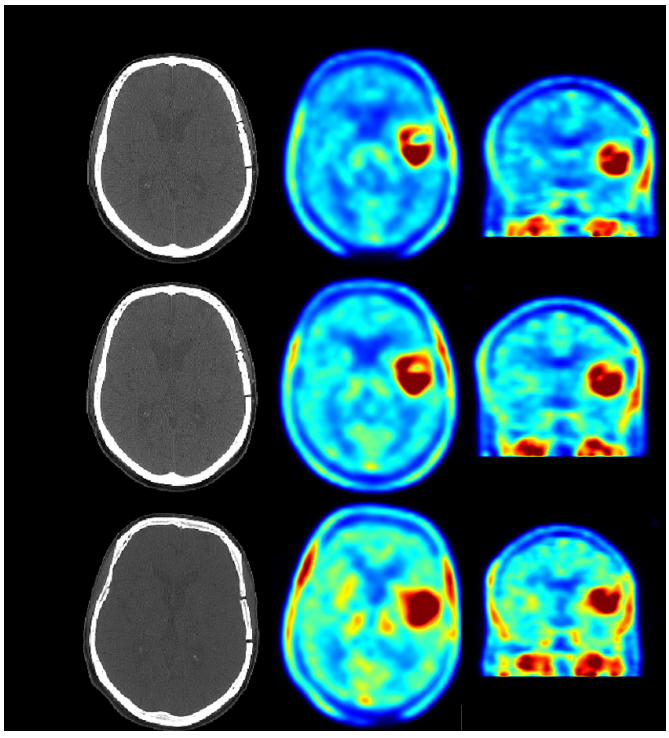

Figure 1 Serial O-(2-[^{18}F]-fluoroethyl)-L-tyrosine positron emission tomography scans including baseline, retest (1 week) and post-therapy.

Study hypotheses, aims, objectives and related end points

Primary aim 1: to quantify the impact of FET on radiotherapy planning volumes relative to MRI alone

The first hypothesis is that incorporation of FET-PET imaging into radiation therapy treatment planning, compared with standard MRI planning alone, will lead to a clinically significant change, defined as >10% change in absolute gross tumour volume (GTV) and/or planning target volume (PTV) for radiotherapy in participants with GBM, particularly in areas lacking BBB disruption.[5] Adjuvant radiation planning is currently performed using predominantly anatomical T1 post-contrast MRI sequences.[11] The volume of residual tumour at the time of initiation of chemoradiation is highly predictive of subsequent patient outcome.[5 7] The most promising nuclear medicine imaging agent is FET, shown to accurately detect the location and extent of GBM in both initial diagnosis and recurrent disease settings. Multiple single-centre studies have shown that the incorporation of FET-PET imaging can lead to significant change and discordance in radiation target volumes for participants with GBM when compared with standard MRI-based radiation planning alone.[6 12–14]

Niyazi *et al*[12] retrospectively compared the MRI-based GTVs to biological tumour volumes (BTVs), based on pathological FET radiotracer uptake, subsequent clinical target volumes (CTVs), and PTVs for the radiotherapy planning of 17 participants with GBM. In 11 cases, there were major differences between GTV/BTV when FET was incorporated with standard MRI-based imaging, with significantly larger FET-based BTVs (median 43.9 cm^3) compared with corresponding GTVs (median 34.1 cm^3). Similarly, Rieken *et al*[13] investigated the volumetric size and uniformity of MRI versus FET-derived GTVs and PTVs of 41 participants with GBM. They reported that the congruence of MRI and FET signals for the identification of glioma GTVs was poor, with mean uniformity indices of 0.39, and furthermore that MRI-based PTVs missed 17% of FET/CT-based GTVs.

Primary aim 2: to demonstrate the accuracy of pseudoprogression assessment using FET

The second hypothesis is that FET-PET imaging will be more accurate than routine MRI and clinical follow-up in differentiating tumour pseudoprogression from true tumour progression.[13 15–18] Chemo-radiotherapy can induce pseudoprogression, defined as progressive enhancing lesions due to treatment-induced changes in

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the BBB, resulting in MRI findings mimicking progressive tumour.[19 20] Pseudoprogression can occur in up to 20–30% of chemoradiation participants and may or may not be accompanied by clinical deterioration.

Despite the advent of the Response Assessment in Neuro-Oncology (RANO)[21] criteria and modified RANO criteria for standard MRI interpretation[22] in high-grade glioma,[23] this remains predominantly criteria used in research and/or clinical trials. Clinically, the interpretation and assessment of disease status remains challenging. Therefore, it is important to have access to improved imaging biomarkers that can more accurately distinguish disease activity from post-therapy changes which enable optimal management decisions. Since FET uptake is independent of a disrupted BBB, this imaging modality may be more sensitive in distinguishing true progression from pseudoprogression. Indeed, FET-PET has been shown to be superior to MRI in detecting pseudoprogression across multiple single-site studies[5 16–18 24 25] and a meta-analysis,[26] but large, prospective multicentre studies are still needed.

Maurer *et al*[24] retrospectively evaluated 127 participants with grade II–IV glioma who underwent FET-PET imaging to distinguish between tumour progression and treatment-related changes who then underwent either re-resection (n=40) or clinical/MRI follow-up. The slope of the time-activity curves (20–50 mins following injection), time to peak activity (objective parameter describing the slope of tracer uptake) and maximum tumour-to-brain ratios (TBRmax) of FET uptake were determined. Treatment-related change was observed in 26% of participants, with an optimal FET-PET TBRmax cut-off value of 1.95 for differentiating tumour progression from treatment-related change (sensitivity 70%, specificity 71%, accuracy 70%). The accuracy of FET PET was significantly higher in isocitrate dehydrogenase (IDH)-wild-type gliomas. The diagnosis based on FET-PET turned out to be incorrect in 33% of the IDH-mutant tumours, but in only 9% of the IDH-wild-type tumours. The FET-PET rating, the WHO grade, the IDH status and the Karnofsky performance status remained independent prognostic factors. O6-Methylguanine-DNA methyltransferase (MGMT) promoter methylation did not significantly affect the diagnostic performance of FET-PET.

The combination of perfusion MRI and FET-PET may improve the diagnostic accuracy in interpreting treatment-related changes. Steidl *et al*[27] evaluated sequential perfusion MRI and FET-PET in 104 participants with WHO grade II–IV glioma and suspected tumour progression. Static (TBRmax) and dynamic FET-PET parameters (slope of the time-activity curves) were calculated, as well as leakage-corrected maximum relative cerebral blood volumes (rCBVmax) from dynamic susceptibility contrast Perfusion Weighted Imaging (PWI). The combined FET-PET parameters (TBRmax and slope) discriminated tumour progression from treatment-related change in 78% of participants, with an rCBVmax cut-off value>2.85 showing a positive predictive value for tumour progression of 100%.

Table 1 summarises the key retrospective and single centre prospective studies addressing the role of FET-PET in radiotherapy treatment planning and in distinguishing pseudoprogression from tumour progression in the management of glioblastoma.

Co-primary outcome

The comparison of the radiation target volume delineation determined by MRI compared with FET-PET imaging.

Co-primary outcome 2

To determine the accuracy and management impact of FET-PET in distinguishing pseudoprogression from true tumour progression and/or tumour recurrence.

Treating clinicians will complete a management intent questionnaire prior to knowledge of the FET-PET3 result, and then again at 4–8 weeks after FET-PET3 results are known, to establish the impact of FET-PET3 on patient management.

Follow-up (6 months later) will be performed to confirm whether final management aligns with that indicated in the post-FET-PET3 management impact questionnaire. This methodology has been previously established as the reference standard for patient management impact assessment of PET imaging studies.

Secondary aim 1: to assess the prognostic value of FET-PET parameters

The third hypothesis is that FET-PET imaging parameters of dynamic uptake, tumour-to-background ratio and metabolic tumour volume will be associated with progression-free survival (PFS) and overall survival (OS). Lundemann *et al*[28] prospectively evaluated 16 participants with GBM undergoing multiparametric [^{18}F]Fluorodeoxyglucose (FDG)-PET, FET-PET and diffusion and dynamic contrast-enhanced MRI at the time of radiation treatment planning. Within the radiotherapy target, median differences of imaging parameters in recurring and non-recurring voxels were calculated for the contrast-enhancing lesion, non-enhancing lesion and normal-appearing grey and white matter. Logistic regression models were created to predict the patient-specific probability of recurrence. The most pronounced correlations were observed for FDG and FET uptake in contrast-enhancing lesions and non-contrast-enhancing lesions. Voxel-wise modelling of recurrence probability resulted in an area under the receiver operating characteristic curve of 0.77 from scans prior to therapy.

Secondary outcomes

1. To investigate the relationships between FET-PET parameters (including dynamic uptake, tumour to background ratio, metabolic tumour volume, radiomics features) and PFS and OS outcomes in glioblastoma.
2. Assessing the change in the blood and tissue biomarkers as determined by serum assay when comparing FET-PET imaging data acquired prior to initial chemo-

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Table 1 Key studies addressing the role of FET in radiotherapy treatment planning and in distinguishing pseudoprogression from tumour progression in the management of glioblastoma

First author	Publication year	Sample size (n)	Study design	Study outcomes/findings
Niyazi[12]	2011	17	Retrospective	FET-PET versus MRI in GTV/BTV for radiation planning.
Rieken[13]	2013	41	Retrospective	FET-PET versus MRI in GTV/PTV for radiation planning.
Hayes[6]	2018	26	Retrospective	FET-PET versus MRI in CTV/BTV for radiation planning.
Lau[30]	2010	21 (n=11 with glioma)	Prospective	Diagnostic value of FET-PET versus FDG-PET in differentiating pseudoprogression from tumour progression: sensitivity 93%, specificity 100%, accuracy 96%, PPV 100%, NPV 91% for FET-PET.
Galldiks[31]	2012	31	Retrospective	Diagnostic value of FET-PET for differentiating recurrence from radiation necrosis: TBRmax accuracy 78%.
Yu[26]	2018	48 studies n=23 in FET-PET	Retrospective meta-analysis	^{18}F-FDOPA and FET-PET to differentiate tumour progression from pseudoprogression: sensitivity 85 versus 82%, specificity 77 versus 80%.
Maurer[24]	2020	127	Retrospective	FET-PET to differentiate tumour progression from pseudoprogression: TBRmax sensitivity 70% and accuracy 81%.
Lohmann[18]	2020	34	Retrospective	FET-PET to differentiate tumour progression from pseudoprogression: TBRmax sensitivity 81% and NPV 80%.
Steidl[27]	2021	104	Retrospective	Sequential PWI MRI and FET-PET to differentiate tumour progression from pseudoprogression: rCBVmax PPV 100%, TBRmax sensitivity 70% and NPV 32%.

BTV, biological target volume; CTV, clinical target volume; FDG, (18)F-fluorodeoxyglucose; FDOPA, ^{18}F-FDOPA (6-[18F]-L-fluoro-L-3, 4-dihydroxyphenylalanine; FET, O-(2-[^{18}F]-fluoroethyl)-L-tyrosine; GTV, gross tumour volume; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; PTV, planning target volume; PWI, Perfusion Weighted Imaging; rCBVmax, maximum relative cerebral blood volumes; TBRmax, maximum tumour-to-brain ratios.

radiation with other prognostic markers of PFS and OS.

3. To look at the relationships of FET-PET versus MRI-determined site/s of progressive disease post radiation and chemotherapy treatment.
4. To estimate the health economic impact of incorporating FET-PET imaging into the management strategy of patients with GBM undergoing chemo-radiotherapy and inthe assessment of post-treatment pseudoprogression or recurrence/progression.

Exploratory aims

There is an unmet need for improved prognostic and predictive biomarkers in GBM. The most validated biomarkers in GBM currently are MGMT promoter methylation and IDH gene mutation. A biobank of serum and /or tumour samples pre-chemoradiation, during-chemoradiation and post-chemoradiation will be subjected to multiomics analyses and the findings will be correlated with FET-PET and MRI radiomics features for the development of multiomics predictive models that may guide optimal therapy in participants with GBM.

Exploratory outcomes

1. Correlation of local and remote central nervous system relapses visualised on FET-PET imaging with radiotherapy treatment parameters (fields, target volumes).
2. Quantification of the differences in dose to normal tissues (including brainstem, chiasm, optic nerves, lenses) resulting from FET-PET planning compared with MRI planning alone.
3. Development of a biobank of serum and/or tumour samples pre, during and post-chemoradiation in participants with GBM and correlate these with FET-PET imaging parameters.
4. A comparison of FET-PET3 to FDG-PET in terms of tumour response assessment.
5. A comparison and correlation of FET-PET with MRI techniques and with histopathology at subsequent

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surgery when performed for suspected tumour recurrence.

METHODS AND ANALYSIS

Study design

The FET-PET in Glioblastoma (FIG) study (TROG 18.06) is a longitudinal prospective, non-randomised, phase II study undertaken in up to 10 metropolitan hospitals around Australia.

Universal Trial Number: U1111-1222-4710. The trial sponsor is Trans Tasman Radiation Oncology Group (TROG) Cancer Research with date of registration: 9 December 2019.

The FIG study aims to recruit up to 210 participants, namely 140 participants in group 1 (pre-chemoradiation); and up to 70 participants in group 2 (post-chemoradiation). Up to 70 additional participants may be recruited into group 2. As the trial focus is imaging-based (rather than a therapeutic intervention), there are no interim analyses planned. The study will received oversight by the FIG Trial Management Committee, as well as the TROG Independent Data and Safety Monitoring Committee and the TROG Scientific Advisory Committee. The first patient was recruited to the study on 27 January 2021 with study recruitment expected to be completed in 2024.

Credentialling procedures

All participating centres must successfully complete pre-trial quality assurance procedures before enrolling participants, including ARTnet (Australasian Radiopharmaceutical Trials Network) validation of all PET scanners. Key credentialling items completed by FIG study sites will be overseen by TROG and cover both radiation oncology and nuclear medicine aspects, outlined in table 2. FET is provided by a commercial manufacturer or produced on-site according to agreed standard operating procedures (SOP). All aspects of FET provision (production, scan acquisition, imaging, etc) are being done in accordance with the joint European Association of Nuclear Medicine (EANM)/European Association of Neuro-Oncology (EANO)/RANO practice guidelines/Society of Nuclear Medicine and Molecular Imaging (SNMMI) procedure standards for imaging of gliomas using PET with radiolabelled AAs and [(18)F]FDG: V.1.0.[10]

Table 2 FIG study—summary of credentialling and quality assurance programme

Radiation therapy quality assurance		
Activity	**Number of cases**	**Comments**
Phantom dosimetry audit	N/A	Evidence of appropriate end-to-end audit using an anthropomorphic phantom to confirm delivered radiation therapy doses
Facility questionnaire	N/A	Documentation of site radiation therapy facilities and processes
Benchmarking exercise—radiation therapy contouring	1	(Part A) Contour a test case using standard imaging to demonstrate understanding of the protocol and ability to meet protocol contouring constraints
Benchmarking exercise—FET-PET imaging interpretation and incorporation into RT target volume delineation	3	(Part B) Delineation of a biological treatment volume using FET-PET imaging (incorporation of the FET-PET volumes into standard MRI-derived target volumes)
Benchmarking exercise—radiation therapy treatment planning	1	Develop a radiotherapy plan using a pre-contoured data set to demonstrate understanding of the protocol and ability to meet protocol planning and dosimetry constraints
Nuclear medicine quality assurance		
Activity	**Number of cases**	**Comments**
ARTnet PET-CT certification	N/A	ARTnet validation of PET and MRI scanners
FIG—technical survey; nuclear medicine and radiology capacities	N/A	Technical survey to determine site imaging facilities and processes
Benchmarking exercise—FET-PET image interpretation target volume delineation	3	Nuclear medicine physician delineation of target volumes using FET-PET imaging
Benchmarking exercise—FET-PET imaging interpretation and response criteria/scoring	3	Nuclear medicine physician interpretation of response criteria, scoring and assessment of disease status using FET-PET imaging

ARTnet, Australasian Radiopharmaceutical Trials Network; FET, O-(2-[^{18}F]-fluoroethyl)-L-tyrosine; FIG, FET-PET in Glioblastoma; PET, positron emission tomography; RT, radiotherapy.

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Table 3 Schedule of assessments in the FIG study

Time point	Registration	Pretreatment	Chemo-RT	Post chemo-RT				Suspected progression on MRI
				4 weeks	4 months (or 18 weeks)	7 months (or 30 weeks)	12 months (or 52 weeks)	
Assessment		Imaging time point 1		Imaging time point 2	(3 months adjuvant TMZ)	6 months adjuvant TMZ)		Imaging time point 3
Visit window	After surgery, prior to chemo-RT		≤7 weeks from surgery	+7 days	±7 days	±7 days	±7 days	+2 weeks from progressive disease on MRI
Informed consent	X							
Eligibility assessment	X							
Clinical assessment ► Performance status. ► Concomitant medications/ therapies. ► Routine blood tests.	X			X	X	X	X	X
Signs and symptoms		X		X				X
EORTC QLQ C30	X		X	X	X	X	X	X
MGMT and biomarker testing		X						
Tissue collection		X						
Serum biomarkers		X		X				X
MRI*		X (MRI1)		X (MRI2)	X *	X *	X *	X (MRI3)
FET-PET†		X (FET-PET1)		X (FET-PET2)				X (FET-PET3)
FDG-PET†								X
Management intent questionnaires								X
Survival status								

*Where feasible, FIG participant MRI are performed as per online supplemental material S3, otherwise MRI protocol as per site standard protocol.
†FET-PET and FDG-PET performed as per online supplemental material S4.
‡
FDG, [^{18}F]Fluorodeoxyglucose ; FET, O-(2-[^{18}F]-fluoroethyl)-L-tyrosine; FIG, FET-PET in Glioblastoma; MGMT, O6-Methylguanine-DNA methyltransferase (MGMT) promoter methylation; PET, positron emission tomography; RT, radiotherapy; TMZ, temozolomide.

Study interventions

Following consent and screening, eligible participants will be offered enrolment at one of 10 credentialled study sites across Australia, as either a Group 1 participant pre-chemoradiation or a Group 2 participant, who enter and undergo FET-PET2 and study MRI2 at one month post-chemoradiation completion.

Adjuvant chemoradiation will be administered as per standard of care and should start after registration and within 7 weeks from the date of surgery. Radiotherapy will consist of conventionally fractionated radiotherapy delivered either as 60 Gy/30 daily fractions over 6 weeks[28] or 40.05 Gy/15 daily fractions over 3 weeks for elderly participants and/or those with poor performance status[3] (see online supplemental material S1). TMZ will be 75 mg/m^2 oral daily for either: (1) 6 weeks concurrent with radiotherapy (60 Gy/30 daily fractions), or (2) 3 weeks concurrent with radiotherapy (40.05 Gy/15 daily fractions) for elderly and/or poorer performance status participants. Once concurrent chemoradiation has been completed, the participant will have a 4-week rest period before commencing adjuvant TMZ.

All participants

Adjuvant TMZ will be administered as per standard of care at 150–200 mg/m^2 days 1–5 every 28 days until either disease progression, unacceptable toxicity or completion of 6 months of treatment. Dose interruptions and/or reductions, as well as ongoing treatment after discontinuation and/or cessation of study treatment is at the discretion of the participant's treating clinician. Concurrent recruitment to other which are TMZ-based therapeutic trials is permitted.

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FET-PET1 (along with study MRI1) will be performed following initial surgery and before starting chemoradiation in Group 1 participants. FET-PET2 (along with study MRI2) will be performed no earlier than 4 weeks (+ up to 7 days) following concurrent chemoradiation in both Group 1 and 2 participants. Study MRI3 will be performed at the time of clinical suspicion of tumour recurrence and/or progression, with FET-PET3 performed within 14 days of suspected radiological progression on MRI in both Group 1 and 2 participants. The timing of FET-PET1 is aligned with literature establishing the potential role of FET-PET in delineating the extent of residual tumour[12,13]). FET-PET2 timing was to establish a baseline after chemoradiation and to compare to FET-PET3 which is timed for when clinical suspicion of progression versus pseudoprogression arises. At the time of suspected recurrent disease, in addition to FET-PET3 and MRI3, study participants are requested to undergo an FDG-PET scan which has been made optional, as although a direct comparison of FDG-PET with FET-PET is planned, the study protocol requirements for participants are already quite substantial, with the FET-PET and MRI taking precedence.

Importantly, treating oncologists and imaging specialists are blinded to FET-PET1 and FET-PET2 results. Furthermore, FET-PET1 results will not be incorporated into actual radiotherapy target volumes used for treatment, given that FET-PET1 is being evaluated for this indication in the study.

Tissue will be obtained at baseline (archival or from debulking surgery) for MGMT methylation status, and at the time of recurrence if repeat surgery and/or biopsy is clinically indicated Formalin-Fixed Paraffin-Embedded(FFPE) samples are sent to the central laboratory). Blood for serum markers is obtained between registration and initial FET-PET, then on the day of each subsequent FET-PET. If further surgical resection or biopsy is required, a sample of the tissue will be requested to assist with confirmation of tumour recurrence versus pseudoprogression. EORTC QLQ C30 will be assessed at baseline (study entry) and at each assessment time point (see table 3, schedule of assessments). All participants will be followed for 12 months after the end of accrual to allow evaluation of PFS and OS, with analysis at 12 months after the final patient has completed chemoradiation treatment.

The FIG study schema is shown in figure 2.

Eligibility

Participants must fulfil all inclusion and none of the exclusion criteria prior to registration and enrolment. Eligibility criteria are listed below.

Inclusion criteria

All participants

- Age ≥18 years.
- Histologically confirmed, newly diagnosed GBM (IDH1-R132H wild type or IDH mutant using immunohistochemistry (IHC) (2016 WHO grade IV glioma) following surgery, with methylated or non-methylated MGMT promoter gene.

Note: Participants with a previous grade I–III glioma which has progressed to GBM are eligible if they have not received prior cranial radiotherapy or TMZ for the treatment of glioma.

- Eastern Cooperative Oncology Group (ECOG) performance status 0–2.
- Life expectancy >12 weeks.
- Adequate bone marrow reserve or organ function to allow TMZ-based chemotherapy.
- Available tissue for MGMT and biomarker analysis.
- Participants capable of childbearing are using adequate contraception.
- Willing and able to comply with all study requirements, including treatment, timing and/or nature of required imaging and study assessments.
- Has provided written informed consent (see online supplemental material S2).

Group 1 participants

- Considered suitable for radiotherapy (with one of the two dose schedules of 60 Gy in 30 daily fractions or 40.05 Gy in 15 daily fractions) plus concurrent TMZ followed by adjuvant TMZ.

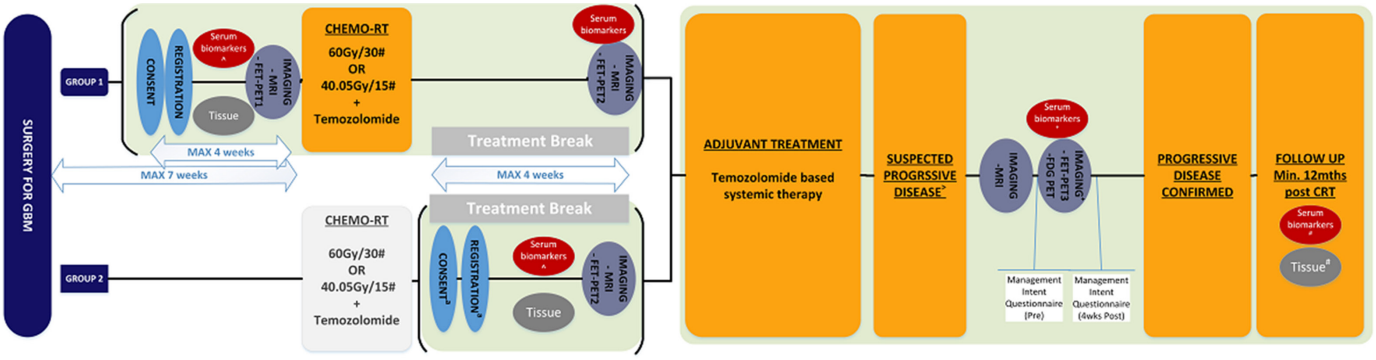

Figure 2 The FIG study schema for screening and registration of both Group 1 (postoperative pre-concurrent chemoradiation) and Group 2 (prior to adjuvant temozolomide) participants. CRT, chemo-RT; GBM, glioblastoma multiforme; FET, O-(2-[^{18}F]-fluoroethyl)-L-tyrosine; PET, positron emission tomography; [^{18}F]Fluorodeoxyglucose (FDG) PET, RT, radiotherapy.

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Group 2 participants (entering the study post chemoradiation at imaging time point 2)

- Currently undergoing or have recently completed concurrent radiotherapy with TMZ, with one of the two radiation dose schedules of 60 Gy/30 daily fractions or 40.05 Gy/15 daily fractions and logistically able to be recruited.
- Have commenced adjuvant chemoradiation ≤7 weeks from surgery.
- Considered suitable for adjuvant TMZ-based chemotherapy.

Exclusion criteria

- Participants with implanted devices deemed by the radiologist to be a contraindication to performing a brain MRI.
- Any concurrent comorbidities, conditions or illness, including severe infection or medical or psychiatric conditions that may jeopardise the ability of the participant to undergo the procedures outlined in this protocol with reasonable safety or that may compromise assessment of key outcomes.
- History of another malignancy within 2 years prior to registration.
  Note:
  - Participants with a history of adequately treated carcinoma in situ, basal cell carcinoma of the skin, squamous cell carcinoma of the skin or superficial transitional cell carcinoma of the bladder are eligible.
  - Participants with a history of other malignancies are eligible if continuously disease free for at least 2 years after definitive primary treatment.

Group 1 participants

- Prior chemotherapy or cranial radiation within the last 2 years.

Outcome measures and assessments

Schedule of assessments

Assessments will be performed according to the schedule shown in table 3 for FIG study Group 1 and Group 2 participants.

Post progression follow-up consists of survival status verification at 1 year post chemoradiation completion and 6 monthly thereafter. For those participants proceeding to second surgery, tissue and serum blood biomarkers will be collected.

Patient and public involvement

Patients were involved in the design and conduct of this research. In particular, there was a consumer investigator named on competitive grant funding applications secured to support the FIG study. In addition, integral input was sought from a consumer representative during the design of the Patient and Information and Consent forms to facilitate a patient-centred approach to informed consent (see online supplemental material S2). A consumer representative is a member of the Trial Management Committee.

FET-PET1 analysis

Following treatment delivery, FET-PET data and FET-PET BTV will be delineated by the site nuclear medicine physician (using the dedicated FIG study V.7.0, MIM software, Workflow). This is sent to the TROG Radiation Therapy Quality Assurance Department for central approval before being made available to the radiation oncologist (RO) for fusion to radiotherapy planning CT and MRI, and delineation of a new PET-MRI defined GTV, CTV and PTV (without reference to actual treatment volumes). Each site will be provided with the FIG trial MIM Workflow (see online supplemental material S5). Central review of RO-derived hybrid volumes are also undertaken.

Table 4 Integrated MRI and FET-PET based treatment response criteria applied in the FIG study

	Treatment predominant	Tumour progression
Static (20–40 min)		
FET-PET activity in lesion	No focal activity	Focal and intense activity in suspected lesion
Compared with FET-PET2	FET-PET3 has similar or less intense activity and distribution	FET-PET3 has more intense or extensive activity
Compared with Gd enhancement on MRI	FET-PET activity concordant with distribution of Gd enhancement	FET-PET activity discordant with Gd enhancement
TBR	TBR<2.3	TBR>2.3
Dynamic (0–40 min)		
Time activity curve (TAC)	Pattern I: slow rising TAC with no identifiable peak	Pattern III: early peak in TAC (<20 min) with subsequent descent pattern

FET, O-(2-[^{18}F]-fluoroethyl)-L-tyrosine; FIG, FET-PET in Glioblastoma; Gd, Gadolinium; PET, positron emission tomography; TBR, tumour to brain ratio.

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FET-PET2 and FET-PET3 analyses for tumour recurrence

An integrated MRI and FET-based treatment response criteria will be used in the FIG study (see table 4). When timepoint 3 is triggered, there is both site and central review of FET-PET3 within seven calendar days of image acquisition (see online supplemental material S6). Treating site clinicians will complete a management intent questionnaire prior to knowledge of the FET-PET3 result and then complete a follow-up questionnaire 4–8 weeks after the FET-PET3 results are known, to establish the impact of FET-PET3 on participant management. FET-PET2 will only be used for comparison to FET-PET3 at the time of evaluation of tumour recurrence/progression for further analysis of lesion uptake, following initial review of FET-PET3 alone.

Time to event, toxicity and QOL measures

Time to event measures are defined as the interval between the date of initial surgery and the date of the event, with censoring at last follow-up if the event has not occurred. The time to first treatment for recurrent disease is defined as the interval between the date of initial surgery and the date of first salvage therapy (eg, re-resection, re-irradiation, second-line chemotherapy or a clinical trial treatment) or death from any cause, with censoring at last follow-up if alive with no treatment for recurrent disease.

As this is an imaging-based study with no therapeutic interventions delivered over and above standard of care, no treatment-related toxicity data will be collected. Only suspected reactions to FET radiopharmaceuticals will be reported as Adverse Events (AE) (collected 48 hours post-FET injection). The incidence of significant toxicities is anticipated to be very low, but could include a local reaction at the tracer injection site or minor systemic symptoms. Study discontinuation would occur in the circumstance that the participant decides to completely withdraw from all aspects of the trial.

Health-related Quality of Life (HRQoL) will be reported by participants using the EORTC QLQ C-30 at baseline (study entry) and at each assessment time point (as per table 2). These will also be used to estimate quality adjusted life years for a comparison with the costs of care including FET-PET delivery, MRI imaging, radiotherapy and outpatient services obtained by consenting participants for access to their administrative claims data (Medicare) for medical and pharmaceutical services use. This data will be used for a health economic analysis compared with published literature.[29]

The cost consequences of incorporating FET-PET imaging in the management of patients with GBM will be evaluated by quantifying the resource use associated with these tests. Data will include resource use associated with the delivery and interpretation of FET-PET scans; chemoradiation and subsequent treatment usage. Resource use associated with all multimodal imaging (FET-PET, MRI) as well as radiation therapy treatment plans will be available from trial-based case report forms. Data on outpatient and community-based services (pharmaceuticals and medical) will also be collected as well as prescribing data. Additionally, based on 10 of the 15 dimensions of the QLQ-C30, the QLU-C10D is a newly developed, cancer-specific multi-attribute utility instrument included in the EORTC assessment system and will be used for the health economic evaluations in cost-utility analyses relating to FIG trial participants.

Tumour and blood will be analysed for multiomics (genomic, epigenomic and transcriptomic) markers including DNA methylation, circulating tumour DNA (ctDNA) and exosomal analysis.

Statistical design

Participant demographic, clinical and treatment characteristics and study outcomes will be presented using standard descriptive statistics (mean, SD and range for continuous variables, frequencies and percentages for categorical variables and Kaplan-Meier method for time-to-event endpoints (PFS/OS). Although there is no formal stratification performed as part of this non-randomised study, analysis of survival outcomes may be adjusted for known prognostic factors including ECOG performance status, age, extent of resection, standard versus hypofractionated radiation course, as well as biological factors including IDH1-R132H (via IHC) and MGMT methylation status.

Primary aim 1

FET-PET1 (Group 1 only) will be used to assess the impact of FET-PET on radiotherapy planning, described using the percentage volume of FET-PET-avid disease that would be excluded from the GTV and PTV participants if MRI data alone were used for GBM radiation treatment planning. If GTV and/or PTV volume changed by >10% in absolute terms (cc^3), it would be concluded that the addition of FET-PET1 has a clinically meaningful impact on radiation planning. The proportion of participants in whom this occurs will be described with a 95% CI. It is anticipated that 140 participants will be available, enabling estimation of the proportion with a 95% CI of maximum width ±8%.

Primary aim 2

FET-PET3 will be used to categorise participants as undergoing pseudoprogression or true tumour progression. This will be compared with the final determination of progression, by clinical follow-up and sequential MRI, and calculating the total proportion of true positives and true negatives. If this accuracy FET-PET is ≤80%, then FET-PET would not be considered sufficiently accurate. If FET-PET3 is obtained in 120 participants, the study has 80% power at 2.5% one-sided alpha to rule out accuracy of 80% if the true accuracy is 90%, and will also enable accuracy to be estimated with a 95% CI of maximum width ±9%.

Secondary aim 1

In this study, use of FET-PET as a prognostic factor for PFS and OS will have power to detect only large differences in

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PFS between groups of participants categorised as having poor (non-responders) or good (responders) prognosis according to the information in FET-PET1. Assuming approximately equal numbers of non-responders and responders in the study, and if the true HR is 1.75 for PFS for FET-PET non-responders relative to responders, then 100 participants followed until progressive disease or death from any cause will enable a difference to be detected with 80% power at 5% (two-sided alpha).

ETHICS AND DISSEMINATION

Ethical and safety considerations

The FIG study was approved by the lead site, Austin Health Human Research Ethics Committee - HREC/56071/Austin-2019. HREA (V.3, 30 December 2019), Protocol (V.1.0, 01 October 2019). Protocol No. TROG 18.06. Other clinical sites will provide oversight through local governance processes, including obtaining informed consent from suitable participants (see online supplemental material 2). Any substantial amendments to the study protocol will be reported to the lead site ethics committee for approval prior to implementation, and updated on the trial registry, with study investigators being advised in writing.

Dissemination plan

The FIG Trial Co-Chairs and Trial Management Committee are responsible for presentations and publications arising from this trial with the TROG Publications Committee providing oversight and independent scientific review of all relevant material prior to submission. Study promotion and updates will be undertaken via relevant professional and consumer networks across Australia. Results will be disseminated in relevant scientific forums, peer-reviewed publications and using a range of media channels including newsletters and social media.

The FIG study publication policy is an overarching policy between participating researchers that governs the multisite collaborative effort. The FIG study will run under the auspices of the FIG Trial Management Committee and be open to input from all participating sites and researchers.

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Competing interests None declared.

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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

Koh E-S, *et al. BMJ Open* 2023; 13:e071327. doi: 10.1136/bmjopen-2022-071327

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.

Koh E-S, *et al. BMJ Open* 2023; 13:e071327. doi: 10.1136/bmjopen-2022-071327

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.

Koh E-S, *et al. BMJ Open* 2023; 13:e071327. doi: 10.1136/bmjopen-2022-071327

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

Koh E-S, *et al. BMJ Open* 2023; 13:e071327. doi: 10.1136/bmjopen-2022-071327

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.

Insert Header with institution's name or institution's letterhead

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

[Insert site name]

Title	**Prospective, Multicentre trial evaluating FET-PET in Glioblastoma (FET-PET in Glioblastoma)**
Short Title	**FIG STUDY**
Project Sponsor	TROG Cancer Research
Coordinating Principal Investigator/ Principal Investigator	*[Coordinating Principal Investigator/ Principal Investigator]*
Location	*[Location]*

Part 1 What does my participation involve?

1. Introduction

You are invited to take part in this clinical study. This is because you have recently been diagnosed with Glioblastoma (GBM). This document tells you about the study and describes what will happen if you decide to take part.

This Participant Information Sheet/Consent form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. You may also take this form away with you. Ask questions about anything that you do not understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or GP.

Participation in this research is voluntary. If you do not wish to take part, you don't have to. You will receive the best possible care whether or not you take part in this study.

If you decide you want to take part in this study, you will be asked to sign the consent form in the consent section. By signing it, you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to the tests and research that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2. What is the purpose of this research?

Glioblastoma (GBM) is the most common primary brain cancer in adults representing over half of all primary malignant (cancerous) brain tumours. Standard treatment for GBM involves surgery followed by combined chemo-radiotherapy and then further post-operative chemotherapy with a tablet called temozolomide.

It is important to understand that the treatment you have and will be receiving is as per usual, i.e. best practice (standard of care). Your treating team will talk with you about what treatment is recommended, the timing of each treatment and the expected side effects. Imaging plays a key role in diagnosis, radiotherapy planning, and monitoring of treatment response inpatients with GBM. The current standard of care imaging is Magnetic Resonance Imaging (MRI) which tells the doctor what the shape and size of the tumour is. A newer form of imaging has been developed using Positron Emission Tomography (PET), where a radiotracer called FET, a chemical compound, is used to detect whether tumour cells are active or not.

It is thought that using FET-PET will help to;

1. More accurately define the tumour and treatment area for radiotherapy planning compared to standard MRI
2. More accurately assess tumour changes versus treatment-related changes which can be hard to interpret with standard MRI scans. This is particularly important in the first 3-4 months after radiotherapy where changes on MRI can be hard to interpret.
3. Help predict the future tumour status and outcome of Glioblastoma after therapy

It is hoped that this new imaging approach, with FET-PET scans, will lead to more accurate assessment, and improve both treatment decisions and outcomes for patients with GBM. Currently FET-PET scans are not part of the routine care for patients diagnosed with GBM.

3. What does participation in this research involve?

To be eligible for this study you must have been recently diagnosed with Glioblastoma (GBM).

If you choose to participate, you will be participating in an interventional single arm study comparing the imaging technique FET-PET to the standard imaging (MRI). Sometimes we do not know which imaging method is best and to find out we need to compare the different imaging methods. The results will be compared to the standard imaging that is MRI to see if one is better.

This Research project has been designed to make sure researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

There are no additional costs associated with participating in this research project, nor will you be paid. The additional scans and medical care required as part of the research project will be provided to you free of charge.

If you decide to participate in this research project, the study doctor will inform your GP.

The main steps involved in the study are:

I. **Agreeing to participate in the study (consenting)**
II. **Registration in to the study**
III. **Undergoing the study scans**
IV. **Follow-Up**

You are welcome to bring a family member or friend to all appointments.

I. **Agreeing to participate in the study (consenting):** Your study doctor will talk to you about the study and if you agree to take part, they will ask you to sign the study consent forms. You will be given a copy of these forms to keep. Any trial specific procedures will only take place after you have signed the consent form.

II. **Registration into the study:** After you have given your consent, your study doctor will arrange for some procedures to be conducted. These procedures will include;

Procedure	Details
Clinical assessment	Your study doctor will ask you about your health, any medications you are taking and the symptoms you are experiencing. You will be asked for a blood test to be collected to check the function of your organs, your blood chemistry and your blood cell count. The study team will record your date of birth, postcode, and other relevant details.
Pregnancy test	If you are a woman of childbearing potential, you will be asked to take a urine pregnancy test.
Health and Quality of Life Questionnaire	You will be asked to complete a questionnaire related to any symptoms you may have and their impact on your day-to-day life. This will take approximately 15 minutes to complete.

You will be allocated to join one of the two groups in the study, which is dependent on what stage you are at in your standard treatment at the time of registration;

- **Group 1 participants** will start the study after their initial surgery for GBM and prior to commencing post-operative chemo-radiation treatment (CRT). It is expected that most study participants will be in this group.
- **Group 2 participants** will start the study after chemo-radiation treatment is completed but before they start their monthly cycles of chemotherapy with temozolomide (TMZ) tablets.

Your study doctor will let you know what group you will be in.

III. **Undergoing study scans:**

FET-PET Scans: These scans will be performed in addition to your usual care. You will be required to have 2 or 3 of these scans, depending on when you joined the study (please see please see Figure 1: FIG flow diagram on page 6).

- Group 1 participants will have a FET-PET1 scan prior to the start of chemo-radiation treatment.
- Both Group 1 and then Group 2 participants will have a FET-PET2 scan performed 4 weeks after completion of chemo-radiation treatment (and before the start of ongoing chemotherapy cycles with Temozolomide tablet).
- Both Group 1 and Group 2 participants will have a FET-PET3 scan. This will be done when your MRI scans shows that the tumour might be becoming active. The exact timing of this scan will likely be different for each participant and will be decided by your treating medical team.

You will need to fast for 4 hours prior to having each FET-PET scan and each scan will take approximately 1 hour. The FET dose is 200MBq +/- 10%.

It is important to understand that the results of both the early, initial FET-PET1 scan (before chemo-radiation) and the FET-PET2 scan (4 weeks after chemo-radiation) will not be immediately shared with your treating specialist team, as they are performed as research scans and will be reviewed by a different panel of specialists. Your standard radiotherapy treatment will not be altered as a result of the FET-PET1 scan.

This study aims to work out which is the best way to interpret these early FET-PET scans and so the results will not be used to immediately change your treatment.

In contrast, as the FET-PET3 scan is done at the time that the tumour might be becoming active, based on the MRI scan appearances at the time, the results of the final FET-PET3 scan will indeed be shared with you and your treating specialist team.

MRI Scans: These scans will be performed as at the same time points during your treatment as you would normally be ordered by your treating specialist team for your standard care. Each MRI will take approximately 40-60 minutes and will be performed with intravenous contrast each time. Your study doctor will discuss the results with you after each MRI scan is done.

FDG-PET scan: This study asks that you undergo a standard FDG PET (using the radiochemical FDG) to provide some additional information to help guide your treatment, if there is concern the brain cancer is becoming active based on your MRI scans. Although it is important that this FDG-PET scan is done as part of the study overall, it is not considered mandatory or essential, so your treating medical team will discuss this with you. This scan will take approximately 2 hours, including the time for the FDG tracer injection and scan.

Biomarker research: The researchers conducting this study are interested in looking for biomarkers (biological molecules found in blood and tissue) to see if there are any relationships between the biomarkers, with the way the GBM tumour responds to the various treatments and the FET-PET and MRI scans that you will undergo. Finding biomarkers can help in the development of future treatments or predict how well a patient with GBM may respond to specific treatments.

For all participants enrolled into this study, tissue and blood samples will be required at certain time points.

- Tumour tissue from your initial surgery will be requested from the original specimen which was removed.
    - Your tumour will be analysed to see if it contains changes to a protein, called MGMT, which may indicate response to the Temozolomide chemotherapy. This test may be conducted at your local institution or, if not available, will be conducted at the *Olivia Newton-John Cancer Research Institute (*ONJCRI) in Victoria. Results of this test will be shared with your treating medical team.
    - Your tumour will also be analysed for other changes within the Ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) (mutations) and other proteins. See section 10 for more details.
- Blood sample:
    - Approximately 50mls of blood be taken at the time of study enrolment and also on the day of some FET-PET scans for analysis of research tumour biomarkers. See section 11 on page 8 for more details for more details.

The biomarker research, apart from the MGMT results, is experimental and will not be suitable for guiding decisions about your treatment. Accordingly, we do not plan to make your individual results from these studies available to your treating medical team.

IV. Follow up:

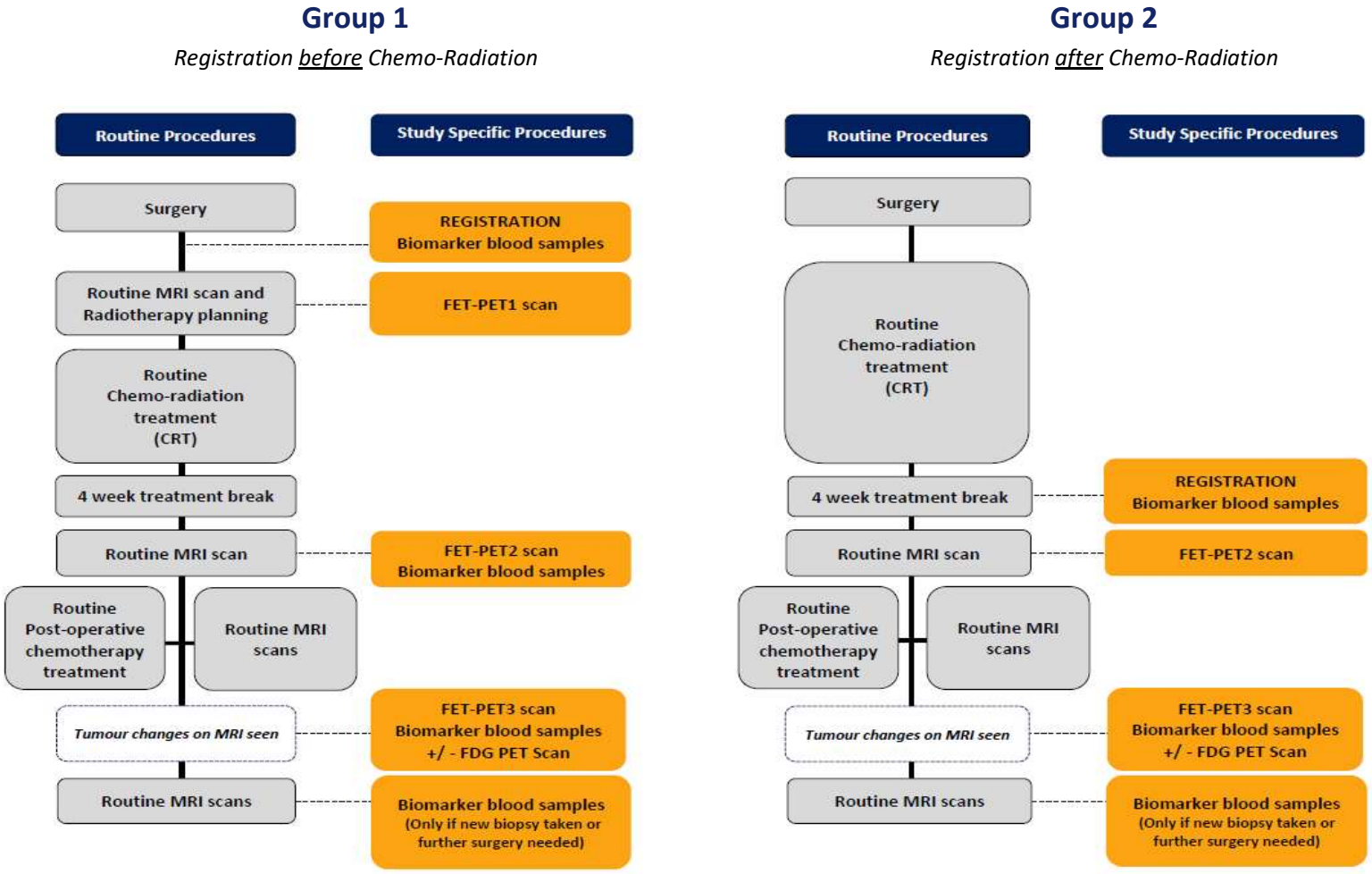
If it is confirmed that your brain cancer has become active again in the future, we would still like to collect information to check on your health status. In the event that you are no longer able to attend clinic appointments, the study team may still collect information about your health via your medical records.

If a further neurosurgical procedure is needed in future, we will request a sample of this tumour tissue and ask you to have another blood sample taken for biomarker analysis at that time if at all possible.

Other assessments:

- **Clinic Assessments:** At 4 weeks, 3 months, 6 months and 12 months after completion of chemo-radiation and at the time that the FET-PET3 scan is done, your study doctor/s will ask you about your health, any medications you are taking and any symptoms you may be experiencing. Your study doctor will also order routine blood tests to check your health. These assessments are part of your standard of care treatment for GBM.
    - **Health and Quality of Life Questionnaire:** During the clinical assessment visits and once in the last week of chemo-radiation (Group 1 participants only) you will be asked to complete a questionnaire related to any symptoms from your brain tumour and their impact on your day to day life. This will take approximately 15 minutes to complete.

Figure 1: FIG flow diagram



4. Medicare and Pharmaceutical data

One of the aims of this study is to look at the resource use and cost effectiveness of FET-PET scans amongst your treatment overall. To do this, at the end of the study, the study doctors would like to assess your data held at the Department of Human Services regarding what medical and pharmaceutical benefits you have accessed 6 months prior to and during your time on the study. This will include such information as health consultations, procedures and tests, the schedule fee for each of these items (e.g. an appointment with your GP or blood tests to monitor your cholesterol level) and the medications you have received.

To allow the study doctors' access to this information, you will be asked to sign an additional consent form when you register into this study and to provide your Medicare number and other details (such as your name and address) needed by the Department of Human Services to make sure the correct information is given to the study doctors. This consent form (or a certified copy) will be sent to the Australian Government Department of Human Services to show that you have consented to the study doctors accessing this information

5. What do I have to do?

If you agree to participate in this study, you agree to be responsible for attending all trial-specific appointments according to our instructions. You also agree to comply with the other conditions in this document. If you cannot, or do not wish to accept this responsibility, then we cannot accept you as a participant in the study. Either way you choose, you will still receive the best possible care whether or not you take part in this study

Your doctor will ask you about procedure or medicines you may be taking. Including any over the counter medications. Please let us know about any changes to these while you are participating in this clinical study.

6. Other relevant information about the research project

This study aims to recruit up to 210 Australian patients with newly diagnosed GBM and will take place among 10 different hospital sites across Australia.

7. Do I have to take part in this research project?

Participation in any research is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you decide to take part, you will be given this participant information and consent form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part then withdraw will not affect your routine treatment, your relationship with those treating you or your relationship with *[Institution]*.

8. What are the alternatives to participation?

You do not have to take part in this study to receive the standard of care treatment for treatment of your GBM at this hospital. This study offers extra imaging to compare the standard MRI imaging with FET-PETs. Standard of care treatment and standard MRIs will still be undertaken if you do not wish to take part in this study. Your study doctor will discuss these options with you before you decide whether to take part in this study. You can also discuss the options with your local GP.

9. What are the possible benefits of taking part?

This research will not potentially provide you with any personal benefit, but the information we collect may reveal important information that may benefit future patients with GBM.

10. What are the possible risks and disadvantages of taking part?

The focus of this study is to understand the benefits of using FET-PET scans in GBM, in addition to routine imaging using MRI scans. To date, no significant side effects have been reported with the use of the FET radiotracer injection (for the FET-PET scans), therefore it is highly unlikely that any significant side effects will occur. The chance of a reaction to the tracer injection is very low. If a possible reaction does occur, this will be managed by a member of the study team. It is unlikely that an 'allergic' reaction would occur after the FET radiotracer injection, and any reaction, even if it does occur, is more likely to be local discomfort at injection site. There may be side effects that the researchers do not expect or do not know about. Please tell your study doctor immediately about any new or unusual symptoms that you may experience, especially in the first two days after the FET radiotracer injection.

This study involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year.

[The effective overall dose from this research project is [insert site mSV] mSv. The dose from this research project is comparable to that received from many diagnostic medical X-rays and nuclear medicine procedures. At this dose level, no harmful effects of radiation have been demonstrated]

The radiological imaging associated with this study is the same as you would normally receive for your care at this hospital.

Having an imaging tracer injected or blood and tissue sample taken may cause discomfort, bruising, minor infecting or bleeding. If this happens, it can be easily treated.

11. What will happen to my test samples?

At your routine blood tests, about 20 mls (1 tablespoon) of blood will be collect to examine your full blood count and biochemistry. These tests will be used to determine your general health status and to screen for a variety of disorders, such as anaemia and infection, as well as nutritional status. These samples are a part of your routine care for your cancer. All blood samples taken for this purpose will be stored and destroyed in line with the Hospital/Pathology lab's policy.

Blood and tissue collected for biomarker research will be stored at the hospital until they are shipped to the central laboratory located at the Olivia Newton John Cancer Research Institute in Victoria. All samples will be coded with your unique study number before being sent. In addition, some samples may also be sent for analysis at other laboratories in Australia and/or the USA, such as Vanderbilt University Nashville Tennessee and Duke University Durham North Carolina. The researchers will not be able to link your samples to your personal information.

Due to rapid advances in technology, it is not possible to predict which exact tests will be available at the time the biomarker research is conducted. The biomarker research may look at mutations in genes involved in the growth of cancer, or in the way that genes affect how your body responds to the treatment. It may also include studying the features of the tumour and the surrounding cells and structures such as blood vessels, immune cells and cells in the connective tissue.

The biomarker research to be undertaken in this study, with the exception of the protein MGMT test results, will not benefit you directly but may help people in the future who have the same kind of cancer as you have. This research is experimental and will not be suitable for guiding decisions about your treatment. Accordingly, we do not plan to make your individual results from these studies available to your doctor.

After this biomarker research has been conducted, we would also like to store any leftover samples for use in any ethically approved future research studies that may or may not be related to this study. This means that your samples would be stored indefinitely or until they are used up. In the future, other doctors and scientists may use your samples to learn about many different diseases and conditions. Their goal is to improve health outcomes and develop new treatments. You will retain the right to have your samples destroyed at any time by contacting your study doctor. If you decide to have your samples destroyed, any data or analyses that were done before the request cannot be removed. However, all of your remaining samples will be destroyed. The researchers will not sell your tissue or blood. You will not benefit financially if this research leads to the development of a new treatment and/or medical test.

12. What if new information arises during this research project?

Sometimes during the course of a trial, new information becomes available about the treatment that Is being studied. If we find something new about an intervention while this study is underway, your study doctor will discuss with you what it means and also discuss whether you want to continue in the study. Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, they will explain the reasons and arrange for your regular health care to continue.

13. Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved.

14. What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research group.

15. Could this research project be stopped unexpectedly?

Yes, if this study is stopped earlier than planned, the study doctor will let you know and explain the reason behind the decision.

16. What happens when the research project ends?

Once the study has finished, it is likely your doctors will still ask you to attend follow up visits to confirm your health status as part of your ongoing care.

Part 2 How is the research project being conducted?

17. What will happen to information about me?

A copy of your signed consent forms will be sent to the TROG Cancer Research central office in Newcastle (NSW), which coordinates the FIG study, for audit purposes. For consent to the main study, all identifying information will be removed, but for the consent to access Medicare and pharmaceutical information, all identifying information will visible, as this is required by the Australian Government, Department of Human Services. By signing the consent form, you are agreeing to this.

Information about your participation in this study will be recorded in your health records and this and other relevant information may be obtained from these records held at this or other health services (such as your GP) for the purpose of this research.

Australian and [insert the name of a state or territory] privacy law gives you the right to request access to your information that the researchers have collected and stored. The law also gives you the right to request corrections to any information about you that you disagree with. Please contact the study team (see section [insert the number of the section containing the study-team contact] of this document) if you would like to access your information.

We will not disclose your information without your permission, except in compliance with the law. Information about you may be obtained from your health records held at this institution and may be obtained from other health services for the purposes of research. Should you wish to cease treatment we would like the option to maintain follow-up. If you sign the consent form, you agree to the study team accessing health records if they are relevant to your participation in this study.

Information concerning your participation in the study will be sent to the TROG Cancer Research central office by the study doctor or their designate. This may include copies of sections of your medical records, medical reports, your radiotherapy treatment plan and imaging scans. This information will only be identified by your initials, date of birth and/or a unique study number. In no instance will the study centre identify you by name on these documents. They have policies of strict confidentiality and will not release any information concerning you, except to other researchers in this study. You will not be identifiable as an individual in any publication resulting from this study.

The re-identifiable/coded (it is possible to use the code to re-identify you) information held by the sponsor however, will not be destroyed. Only the study team at [insert site name] will be able to re-identify you from the code.

It is anticipated that the results of this study will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be personally identified.

18. Data sharing

Information collected during the study, which can include any imaging, will be stored indefinitely as it may be utilised in future research by the study investigators, study sponsor and collaborating researchers to advance our knowledge about cancer and its treatments. This may involve combining the data collected from multiple related trials in Australia and from around the world. If this happens, anonymised information about you may be passed to these researchers, they would not be able to identify you from the information provided.

MBS and PBS data collected during this study will not be used for future research.

19. Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

20. Who is organising and funding the research?

This research study is being sponsored by the Trans Tasman Radiation Oncology Group (t/a TROG Cancer Research), a not-for-profit research group involving many cancer researchers in Australia, as well as internationally. This study has been awarded funding by the Medical Research Future Fund, Cure Brain Cancer Foundation and the Australian Brain Cancer Mission / Cancer Australia.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to TROG Cancer Research, the study doctors or their institutions, there will be no financial benefit to you or your families from these discoveries.

No member of the research team will receive a personal benefit from your involvement in this study (other than their ordinary wages).

21. Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this study has been approved by the HREC of Austin Health.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interest of people who agree to participate in human research studies.

22. Further information and who to contact

We have included several contacts for you below. Who you contact depends on what information you need:

Treating Hospital contact person

Name	[Name]
Position	[Position]
Telephone	[Phone number]
Email	[Email address]

If you wish to discuss the study or with someone not directly involved, particularly in relation to matters concerning policies, information or complaints about the conduct of the study or your rights as a participant, you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Austin Health Human Resources Ethics Committee
Position	Mrs Lisa Pedro
Telephone	(03) 9496 4035
Email	ethics@austin.org.au

Local Research Office contact

Contact	[Position]
Telephone	[Phone number]
Email	[Email address]

Insert Header with institution's name or institution's letterhead

Consent Form - *Adult providing own consent*

Title	**Prospective, Multicentre trial evaluating FET-PET in Glioblastoma (FET-PET in Glioblastoma)**
Short Title	**FIG Study**
Project Sponsor	TROG Cancer Research
Coordinating Principal Investigator/ Principal Investigator	*[Coordinating Principal Investigator/ Principal Investigator]*
Location	*[Location where the research will be conducted]*

Consent Agreement

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *[Name of Institution]* concerning my disease, medical history and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that the sponsors of this study may make my data available to other researchers for future research. Any data transferred to a third party for future research will remain coded with my unique number and will not contain my personal information. I give permission for these individuals to have access to my data.

I consent to my treating doctor/s being notified of my participation in this study and any clinically relevant information noted by the study doctor in the conduct of the study.

I consent to the storage and use of blood and tissue samples taken from me as described in the Participant Information Sheet, for any future extended research (this research may include genetic testing).

I understand that I will be given a signed copy of this document to keep.

Koh E-S, *et al. BMJ Open* 2023; 13:e071327. doi: 10.1136/bmjopen-2022-071327

Declaration by Participant

Name of Participant (please print) _____

Signature _____ Date _____

Under certain circumstances, a witness* to the informed consent is required *(see Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 at 4.8.9)*

Name (please print) _____

Signature _____ Date _____

* Witness is not to be the Investigator, a member of the study team or their delegate. Witness must be 18 years or older.

If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

Declaration by Study Doctor/Senior Researcher†

I have given an explanation of the clinical study, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Declaration by Interpreter (if applicable)

I am a qualified interpreter. I have given an explanation of the research project, its procedures and risks and I believe that the patient has understood that explanation.

Name of Interpreter (please print) _____

Signature _____ Date _____

Note: All parties signing the consent section must date their own signature.

Insert Header with institution's name or institution's letterhead

Consent Form – MBS/PBS information

Title	**Prospective, Multicentre trial evaluating FET-PET in Glioblastoma (FET-PET in Glioblastoma)**
Short Title	**FIG Study**
Project Sponsor	TROG Cancer Research
Principal Investigator	[Principal Investigator]
Location	[Insert site name] [Location]

Note: All parties signing the consent section must date their own signature.

Important Information

Complete this form to request the release of personal Medicare claims information and/or PBS claims information to the FIG Study.

Any changes to this form must be initialled by the signatory. Incomplete forms may result in the study not being provided with your information.

By signing this form, I acknowledge that I have been fully informed and have been provided with information about this study. I have been given an opportunity to ask questions and understand the possibilities of disclosures of my personal information.

PARTICIPANT DETAILS

1. Mr ☐ Mrs ☐ Miss ☐ Ms ☐ Other ☐

Family name: _____ First given name: _____

Other given name (s): _____

Date of birth: DD / MM / YYYY

2. Medicare card number: _____

3. Permanent address: _____

Postal address (if different to above): _____

Koh E-S, *et al. BMJ Open* 2023; 13:e071327. doi: 10.1136/bmjopen-2022-071327

AUTHORISATION

4. I authorise the Department of Human Services to provide my:

☐ Medicare claims history OR

☐ PBS claims history OR

☐ Medicare & PBS claims history

for the period* DD / MM / YYYY to DD / MM / YYYY to the FIG Study.

**Note: The Department of Human Services can only extract 4.5 years of data (prior to the date of extraction), the consent period above may result in multiple extractions.*

DECLARATION

I declare that the information on this form is true and correct.

Signed: _____ (participant's signature)

Dated: DD / MM / YYYY

OR

Signed by _____ (full name)

_____ (signature) on behalf of participant

Dated: DD / MM / YYYY

☐ Legal guardian**

☐ Power of attorney** ☐ Guardianship order**

**Once a young person has turned 14 years old, they must consent to their own information being released*

*** Please attach supporting evidence*

APP 5 – PRIVACY NOTICE

Your personal information is protected by law (including the Privacy Act 1988) and is collected by the Australian Government Department of Human Services for the assessment and administration of payments and services.

Your information may be used by the department, or given to other parties where you have agreed to that, or where it is required or authorised by law (including for the purpose of research or conducting investigations).

You can get more information about the way in which the department will manage your personal information, including our privacy policy at humanservices.gov.au/

Power of attorney – A power of attorney is a document that appoints a person to act on behalf of another person who grants that power. In particular, an enduring power of attorney allows the appointed person to act on behalf of another person even when that person has become mentally incapacitated. The powers under a power of attorney may be unlimited or limited to specific acts.

Guardianship order – A Guardianship order is an order made by a Guardianship Board/Tribunal that appoints a guardian to make decisions for another person. A Guardianship order may be expressed broadly or limited to particular aspects of the care of another person.

A sample of the information that may be included in your Medicare claims history:

Date of service	Item number	Item description	Provider charge	Schedule Fee	Benefit paid	Patient out of pocket	Bill type
20/04/09	00023	Level B consultation	$38.30	$34.30	$34.30	$4.00	Cash
22/06/09	11700	ECG	$29.50	$29.50	$29.50		Bulk Bill

Scrambled ordering Provider number*	Scrambled rendering Provider number*				Hospital indicator	Item category
	999999A				N	1
999999A	999999A				N	2

* Scrambled Provider number refers to a unique scrambled provider number identifying the doctor who provided/referred the service. Generally, each individual provider number will be scrambled and the identity of that provider will not be disclosed.

A sample of the information that may be included in your PBS claims history:

Date of supply	Date of prescribing	PBS item code	Item description	Patient category	Patient contribution (this includes under copayment amounts**)	Net Benefit (this includes under copayment amounts**)	Scrambled Prescriber number*
06/03/09	01/03/09	03133X	Oxazepam Tablet 30 mg	Concessional Ordinary	$5.30	$25.55	9999999
04/07/09	28/05/09	03161J	Diazepam Tablet 2 mg	General Ordinary	$30.85		9999999

Form Category	ATC Code	ATC Name
Original	N05 B A 04	Oxazepam
Repeat	N05 B A 01	Diazepam

* Scrambled Prescriber number refers to a unique scrambled prescriber number identifying the doctor who prescribed the prescription. Generally, each individual prescriber number will be scrambled and the identity of that prescriber will not be disclosed.

** Under co-payments can now be provided for data after 1 June 2012

Insert header with your institution's name or institution's letterhead

Withdrawal of Participation

Title	**Prospective, Multicentre trial evaluating FET-PET in Glioblastoma (FET-PET in Glioblastoma)**
Short Title	**FIG Study**
Project Sponsor	TROG Cancer Research
Principal Investigator	[Principal Investigator]
Location	[Insert site name] [Location]

Declaration by Participant

I wish to withdraw my participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with *[Institution]*.

I consent that any further information collected in my routine care be used in the above research study.

Yes ***No***
(please tick)

☐ ☐

Name of participant (please print) _____

Signature _____ Date_____

Declaration by study doctor/senior researcher†

I have given a verbal explanation of the implications of withdrawal from the trial and I believe that the participant has understood that explanation

Signature _____ Date_____

Name of study doctor/ researcher† (please print) _____

† A senior member of the research team must provide the explanation of, and information concerning, this research study.

Note: All parties signing the consent section must date their own signature