3/4/2019

BRITER protocol

IRAS ID 216343

This protocol has regard for the HRA guidance and order of content

FULL/LONG TITLE OF THE STUDY

Brain Imaging to predict Toxicity in Elderly patients after Radiotherapy

SHORT STUDY TITLE / ACRONYM

BRITER study

PROTOCOL VERSION NUMBER AND DATE

Protocol version 0.8 03/04/2019

RESEARCH REFERENCE NUMBERS

IRAS Number:	216343
SPONSORS Number:	Generated by the Sponsor. Enter if applicable
FUNDERS Number:	Generated by the funder. Enter if applicable

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

.....

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STUDY SUMMARY

Study Title	Brain Imaging to predict Toxicity in Elderly patients after Radiotherapy
Internal ref. no. (or short title)	BRITER study
Study Design	Observational cohort imaging study
Study Participants	Patients newly diagnosed with glioblastoma aged ≥ 65 years undergoing radiotherapy treatment
Planned Size of Sample (if applicable)	100 patients
Follow up duration (if applicable)	6 months
Planned Study Period	2 years
Research Question/Aim(s)	Can you use MRI derived imaging parameters to predict the degree of side effects in patients receiving cranial radiotherapy as treatment for Glioblastoma Multiforme?

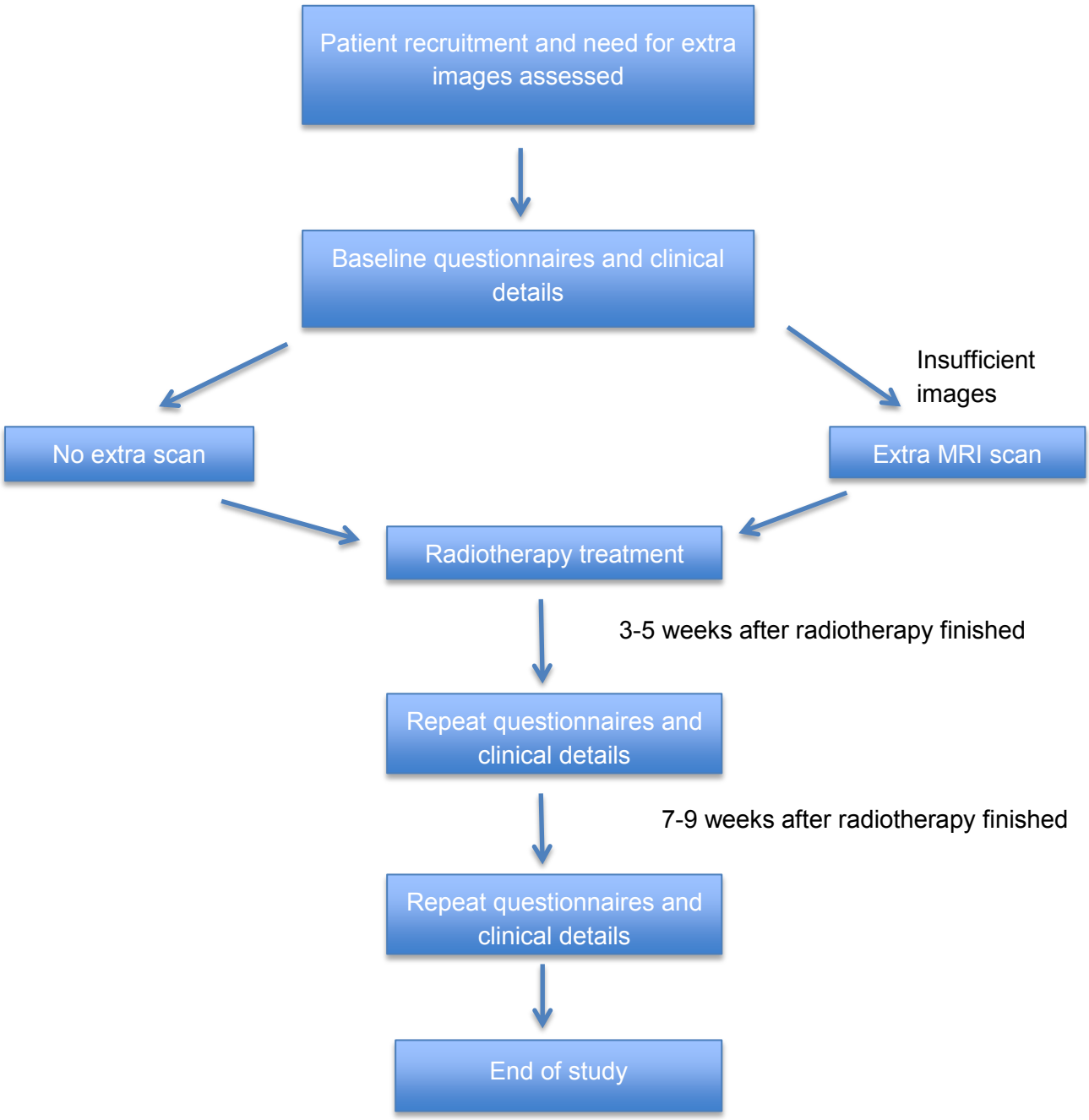
FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Sussex Cancer Fund c/o Julia Lenton Royal Sussex County Hospital Bristol Gate Entrance Eastern Road Brighton BN2 5BE	Funded the total cost of the study - £62,000

PROTOCOL CONTRIBUTORS
The protocol has been written by Dr Cressida Lorimer with contributions and approval from Drs Brock, Saran, Mills and Prof Chalmers

KEY WORDS: Glioblastoma, Radiotherapy toxicity, Geriatric Oncology

STUDY FLOW CHART



STUDY PROTOCOL

Brain Imaging to predict Toxicity in Elderly patients after Radiotherapy

1 BACKGROUND

Glioblastoma (GBM) is the commonest primary malignant brain tumour among the adult population with approximately 2,000 new cases diagnosed in the UK per year. Incidence peaks in the 7th and 8th decades of life and as our global population ages, rates are increasing. Outcomes from this disease remain poor with median life expectancy in the range of 12-18 months, dropping to 3-6 months in the older population[i]. The reasons for this are multifactorial, including more aggressive tumour biology in the older age group, decreased tolerance to treatment related side effects and the potential of under treatment by doctors within the older age group.

Given the poor prognosis in this group, treatment must be balanced against side effects and worsening quality of life. In patients aged 65 or over there is a lack of consensus on standard of care. Radiotherapy has a survival advantage over best supportive care[ii] however the optimal dose of radiotherapy is yet to be established[iiiivv]. A recent Phase III trial randomised elderly GBM patients to standard radiotherapy with 60Gy in 30#, hypofractionated radiotherapy of 34Gy in 10# or temozolomide (TMZ) chemotherapy alone. For patients older than 65, survival was significantly longer with TMZ or hypofractionated radiotherapy than with standard radiotherapy[vi]. Those with defects in the DNA repair protein MGMT did significantly better in the chemotherapy arm than those with intact MGMT, a result which was replicated in the NOA-08 trial which randomised elderly GBM patients to standard radiotherapy with 60Gy in 30# or TMZ alone. This non-inferiority trial showed TMZ to be a suitable monotherapy option, with greater effect seen in those with MGMT promoter methylation[vii]. Recently published evidence has shown a survival benefit from adding concomitant and adjuvant TMZ to a hypofractionated radiotherapy regime of 40Gy in 15# in patients aged over 65, again with greater effect seen in those with MGMT promoter methylation[viii]. There is therefore now evidence to support the use of concomitant chemoradiotherapy or chemotherapy or radiotherapy as single agents amongst elderly GBM patients and an increasing interest in using MGMT promoter methylation status as a biomarker. However there remains a paucity of data surrounding the clinical and radiological basis by which individual patients are assessed for treatment.

The majority of GBM patients over 65 who are actively treated by oncologists receive some form of radiotherapy to the brain. Short term side effects from radiotherapy include fatigue, headache, cognitive defects, nausea, weakness and a need for increased steroid doses. Longer term side effects include persistent cognitive defects, long term fatigue and hormonal imbalances[ix]. Radiation causes an inflammatory response within the brain tissue as well as disrupting the blood brain barrier. It affects the vasculature of the brain with endothelial cell damage leading to microvascular dilatation, thickening of the vessel wall and increased risk of microbleeds and ischemic strokes in the months to follow[x]. There is a risk of inducing tissue necrosis from occlusion of small blood vessels within the brain parenchyma, leading to coagulation, focal necrosis and demyelination. Animal models have suggested radiation is cytotoxic to developing neuroglial progenitor cells with areas of stem cells such as the hippocampus and periventricular zones, particularly vulnerable to damage, leading to longer term neurocognitive decline[xixii]. There is evidence to suggest that radiotherapy can stabilise or improve functional ability for some older patients with GBM aswell as providing a survival advantage however

clinical experience shows that the degree of side effects experienced and their impact on quality of life varies widely within this patient cohort.

Risk factors for toxicities from radiotherapy include dose, fractionation and age however we have no more accurate ways of predicting which patients are more likely to suffer side effects. MRI has been shown to accurately pick up microhaemmorhages and other ischemic changes which may correlate with a 'vulnerable' brain pre-treatment[xiiixiv]. These MRI changes have been examined in Alzheimer and dementia research with correlations shown between MRI markers and disease severity[xv], however they have not yet been used within the neuro oncology setting.

We aim to examine the relationship between MRI markers of a 'vulnerable' brain and degree of acute side effects and change in quality of life amongst a population of older patients being treated with cranial radiotherapy for GBM.

2 RATIONALE

The poor prognosis of older GBM patients leads to an emphasis on the need for focusing on quality of life when deciding on treatment regimes. We have pathological markers which can help us determine sensitivity of the tumour to chemotherapy however we have no such guidance when it comes to making decisions about radiotherapy. If we were able to predict the degree of side effects likely to be experienced by a patient from radiotherapy treatment then it would enable us to make more individually tailored, patient centred treatment plans.

We aim to see if analysis of pre-radiotherapy MRI scans including T2 gradient echo and susceptibility weighted imaging sequences can correlate with acute treatment related toxicity and quality of life amongst patients aged 65 or over undergoing partial brain radiotherapy for GBM. As these patients have an average life expectancy of 3-6 months within the UK we are focussing on acute rather than long term side effects of radiotherapy.

MRI sequences will be utilised to determine any markers of background subclinical microvascular or degenerative disease in the normal brain including microhaemorrhage secondary to hypertension or cerebral amyloid angiopathy and atrophy with cortical volume measurement of the contralateral hemisphere. Additional susceptibility weighted sequences will be performed to identify the presence of microhaemorrhages in the contralateral normal-appearing brain parenchyma. These will be semi-quantitatively assessed using a modified established microhaemorrhage scoring methodology. Absolute measures of the contralateral normal-appearing hemisphere cortical volumes will be acquired using FSL freesurfer software and a volumetric T1 weighted acquisition. These techniques will give us a number of quantitative scores that can then assessed for correlation with changes in quality of life and toxicity scoring systems.

3 THEORETICAL FRAMEWORK

Older patient with a GBM have an average prognosis of 3-6 months. Treatment options are universally palliative and should be aimed at improving or maintaining quality of life for the reminder of these patients' lives. Treatment decisions therefore need to be based around an informed conversation with the patient of the balance between survival benefit and side effect profile. Clinical trials have shown

efficacy of single agent radiotherapy or chemotherapy or short courses of concurrent chemoradiation. Molecular markers have been developed which can help guide decisions regarding the likely efficacy of chemotherapy however no such marker exist for decisions regarding radiotherapy.

Radiotherapy is an effective palliative treatment for GBMs and has been shown in clinical trials to maintain or improve health related quality of life. However outside of a clinical trial population, usual clinical practice reveals some patients in whom the side effect profile from cranial radiotherapy is intolerable and has a significant detrimental effect on patients' quality of life for their remaining short lifespan. The BRITER study aims to examine whether analysis of pre-treatment MRI scans in this cohort could help to predict who is more vulnerable to these side effects and therefore reveal a group of patients in whom single agent chemotherapy or best supportive care would be better treatment options.

4 RESEARCH QUESTION/AIM(S)

4.1 Objectives

The BRITER study is being performed in patients aged 65 or over who have a new diagnosis of GBM. It tests the hypothesis that there is a relationship between 5 scores of a 'vulnerable' brain seen on pre-treatment MRI and a clinically significant change in patient quality of life, as defined by a 10 point change in the EORTC QLQ questionnaire from baseline to 8 weeks post treatment.

4.2 Outcome

The primary outcome is the proportion of patients with a 10 point change in the EORCT QLQ C30 quality of life questionnaire (with the BN-20 brain and ELD14 elderly patient subsets of questions added) from baseline to 8 weeks.

The impact of side effects from cranial radiotherapy will also be assessed by the secondary outcomes of

- MOCA cognitive screening questionnaire
- use of corticosteroids
- degree of grade 3-5 CTCAE toxicity
- overall and progression free survival

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

The BRITER study is an observational cohort study. Eligible patients will be identified during the multidisciplinary team meeting by the participants' usual care team. They will have previously been informed of their diagnosis and then will meet a member of the oncology team to discuss treatment options. Once it has been decided with them by their usual care team that they are to have radiotherapy treatment, they will be given a PIS. After the patient has had sufficient time to read the PIS and have any questions answered by a member of the study team they will be asked to complete a consent form. They will also undergo the baseline clinical assessments prior to starting any

radiotherapy treatment. This will be done during the outpatient appointment with the neuro oncology team.

Baseline clinical assessment of the patients will be conducted in the NHS neuro–oncology outpatient clinic setting. These will involve the EORTC-QLQ-C30 quality of life questionnaire with the BN-20 brain and ELD14 elderly patient subsets of questions added, the MOCA questionnaire (please see Appendix for examples of these questionnaires) and a record of the amount of corticosteroid the patient is currently taking. The EORTC-QLQ-C30 quality of life questionnaires are designed to be completed by the patient (they are allowed to ask for help completing from family/carer) and could therefore be taken home by the patient or completed in the waiting room rather than being completed within the clinic. There is a risk of the questionnaires not being filled in and posted back if participants forget. We have costed for stamped addressed envelopes to be given to the patients in order to post the questionnaires back. The study team (who know the participant and would usually speak to them on the phone anyway during their treatment pathway) are able to call the participant to remind them to post back the questionnaires. The MOCA is administered by a member of the study team.

The original copies of these questionnaires will be in the CRF, alongside details of the participant's age, gender, comorbidities, treatment plan and social situation which will be recorded by the study team.

In most cases, the participant will have undergone an MRI scan as part of their usual care plan prior to attending the neuro-oncology clinic. If this scan has the required imaging sequences needed for the BRITER protocol then no further scanning is required. This will be assessed by the neuro oncology consultant during the outpatient clinic appointment or a member of the study team prior to the appointment. A list of the required sequences will be readily available for the study team during this process. If not all of the required sequences were completed then the patient will undergo a further MRI scan. This will be done prior to the participant starting radiotherapy treatment but should not delay the start of their radiotherapy treatment. Depending on local guidelines, this scan will either take place on the same site or may require travel to another site. Travel costs will be covered for the patient and carer to attend the extra MRI scan.

The participant's treatment plan is not affected by enrolment in the study. The participant will then complete their radiotherapy treatment as planned. When they attend for their routine 4 week post-treatment follow up to the NHS neuro-oncology clinic they will repeat the EORTC-QLQ-C30 quality of life questionnaires and MOCA questionnaire as well as having assessment of their CTCAE radiotherapy toxicity score and steroid use. Again the EORTC-QLQ-C30 quality of life questionnaires could be sent to the patient in advance to complete prior to the clinic appointment or taken home and posted back. If the patient is unable to come to a clinic appointment during the required time frame they can be posted a questionnaire and send it back. The questionnaires should be completed within 3 to 5 weeks after treatment has finished. These will be recorded in the CRFs. Members of the study team are permitted to phone the patient to remind them to complete the questionnaires if they are not returned or can complete them over the phone with the patient. This would normally be done by the CNS or doctor who the patient will already know as part of their usual care team and would be accustomed to speaking to on the phone.

When participants attend for their routine 8 week (plus or minus 1 week) post-treatment follow up to the NHS neuro-oncology clinic they will repeat the same questionnaires and toxicity assessment. At this point their participation in the study is complete.

At the end of the study the results of the questionnaires from the CRFs will be transcribed into a database using Microsoft Excel. The CRFs will not contain the patient's name or recognisable patient details and the database will therefore be pseudo anonymised. A score of 24 or less on MOCA will be deemed abnormal. A change in baseline of 10 points or more on the EORTC-QLQ-C30 quality of life questionnaires will be deemed significant.

The MRI scans for the participants will be anonymised using the patient study ID and electronically transferred to Dr Samantha Mills, neuroradiologist The Walton Centre in Liverpool, for analysis. The following MRI sequences are ideally required:

- Axial T2 4mm slice thickness
- Volumetric T1 pre contrast (1mm or below)
- Post contrast volumetric T1 (1mm or below)
- DWI/ADC (4 mm slice thickness)
- Susceptibility weighted imaging (acquired volumetrically typically in the region of 1.5mm slice thickness but will vary with scanner setup)
- 3D volumetric inversion recovery or MP-RAGE (additional sequence - to allow accurate quantification of cortical thickness/volumes using Freesurfer software in addition to scoring methods of atrophy, must be acquired at 1mm or below)
- Axial T2* gradient echo (4mm slice thickness)

The scan thickness and sequences performed may vary slightly between sites however prior to opening the sites will confirm they can produce the necessary sequences for Dr Mills to produce 5 quantitative scores (tumour volume, contralateral hemispheric brain volume, contralateral cerebral hemisphere cortical thickness, microhaemorrhage score and white matter hyperintensity score) from the images which reflect the degree of potential vulnerability of the brain to the side effects of radiotherapy. These will then be analysed in relation to the clinical questionnaires, steroid usage and grade 3-5 CTCAE radiotherapy toxicity score using SPSS. Multivariable logistic regression models will be fitted to look for significant ($P<0.05$) relationships between the 10 point change in EORTC QLQ quality of life questionnaires and the MRI parameters. Exploratory statistical analysis of the relationships between the MRI parameters and the secondary endpoints will be performed although the study is not powered to detect statistically significant relationships between these.

The creation of the database and statistical analysis of the results will be performed by the CI with the help of a research assistant.

6 STUDY SETTING

The study is a multicentre study and will be run within a number of UK NHS neuro oncology outpatient Trusts. The imaging analysis will be done remotely at the Walton Centre, Liverpool. The Trusts involved all have a neuro-oncology outpatient clinic where the patients will be approached and reviewed as part of the study. They also have appropriate MRI scanners attached to the trusts for the type of imaging sequences that are required. The local protocols for which MRI sequences are performed are slightly different in each trust which is why some patients may require an extra MRI scan.

The recruitment process is similar in each site however the location of the MRI scanners differs slightly. In sites where the MRI scanner is not on the same trust as the outpatient clinic, the costs of taxi journeys to the scanner and back will be covered.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

7.1.1 Inclusion criteria

- Patients aged ≥ 65 years with a new diagnosis of GBM. Diagnosis made via histological confirmation following biopsy or debulking surgery or radiologically during an MDM meeting confirmmed by a consultant neuro radiologist. This lower age limit is due to previous clinical trials which have established gold standard treatment regimes for patients under the age of 65. Patients aged 65 or over have less clinical trial data available to them and treatment decisions are more nuanced with a greater emphasis on quality of life given the poorer prognosis of older patients.
- Patients undergoing radiotherapy treatment to the brain for treatment of their GBM
- Patients able to undergo an MRI scan
- Patients undergoing treatment at one of the study centres
- Patient have capacity to participate in the study
- Patients with physical impairments that prevent them filling in their questionnaires involved in the study may still participate if they are able to communicate their answers though a third party

7.1.2 Exclusion criteria

- Patients not fit for radiotherapy treatment or having single agent chemotherapy with no radiotherapy
- Patients lacking capacity
- Patients who do not have sufficient grasp of the English language to be able to complete the questionnaires
- Patients unable to communicate their responses to the questionnaires
- Patients who are concurrently enrolled in a Clinical Trial of an Investigational Medicinal Product (CTIMP)

7.2 Sampling

7.2.1 Size of sample

Sample size calculations have been performed assuming a clinically significant end point of a 10 point change (SD=22.1 taken from the EORTC website reference guide) in EORTC QLQ questionnaire score between baseline and 8 weeks. Estimated sample size for one-sample comparison of proportion to hypothesized value assuming a 2 sided alpha of 0.05 and power of 0.9 gives a sample of

73. However, allowing for 20% attrition in questionnaire completion, this results in a sample size of 91. With 73 patients at 8 weeks, we will have 90% power for 5% significance to detect 5% of patients achieving a 10 point change in QoL. However, this small a proportion will only allow us to fit one variable in the model. It has therefore been recommended by the statistical team to aim for a recruitment target of 100 patients in order to fit the 5 MRI variables to the model.

Patients who are enrolled within CTIMP studies will not be eligible to be recruited into the study as they would introduce too many unknown variables for adequate statistical analysis with a cohort of this size.

Previous work done by this study group has shown this is a feasible recruitment target over 2 years.

The study team will review recruitment at 9 months and if it has not reached 25% then they will explore ways to increase recruitment, including opening at other sites.

7.2.2 Sampling technique

The sample aims to cover all eligible patients presenting over a 24 month period across **a number of** NHS Trusts. Retrospective work the study team has carried out has shown that it is feasible to achieve the required sample size during this time period however is recruitment is poor then there is scope to expand to other sites or to extend the duration of the study period. The different trusts are located across the UK and should produce an unselected cohort in terms of gender, educational achievement and socioeconomic background.

7.3 Recruitment

7.3.1 Sample identification

Eligible participants will be identified from weekly multidisciplinary team meetings (MDTs). These are attended by the usual clinical neuro oncology care team for the patient who will also make up the study team, thus no one outside of the usual care team will have access to patient identifiable data. The patient lists for the MDTs will be examined and patients meeting the eligibility criteria for the study will be identified.

No public recruitment (i.e. posters/leaflets/website) will be performed. It is UK practice that all newly diagnosed GBM patients must be discussed at a relevant MDT meeting. Participants will be attending for their usual NHS neuro oncology clinic appointment when they are recruited. The follow up assessment will also be done during their routine NHS follow up appointments. The only potential extra appointment would be if the patient requires an additional MRI scan. In these cases the travels costs for the participant and carer will be covered within reason.

7.3.2 Consent

Eligible participants will be approached at or soon after their initial neuro oncology outpatient clinic appointment after it has been confirmed that they are eligible for the study (i.e they are to undergo radiotherapy treatment for treatment of their GBM). Treatment decisions are made prior to enrolment

within the study and are not affected by the study. Capacity assessments will be undertaken during this clinic appointment by a member of the clinical or study team who has the appropriate training prior to enrolment within the study. Capacity will be reassessed at each subsequent follow up (4 week and 8 week post treatment appointments). If participants lose capacity the participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant. This is outlined in the patient information sheet.

Eligible participants will be given a patient information sheet and adequate time to read and discuss any queries with a member of the study team during their outpatient consultation. If they agree to participate in the study then they will complete a written consent form. This consent form will include permissions for the study team to access their clinical records and pathological samples as well as performing the extra MRI sequences. The consent form will be received by a member of the study team (usually the oncology consultant or nurse specialist) during the outpatient consultation.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Assessment and management of risk

Risk of significant harm to the participant is unlikely within this study. Participants who require a further MRI scan may require the administration of gadolinium contrast. This is generally safe and well tolerated however the risk profile of this will be discussed with the patient prior to administration and local policies will be followed if the patient has a reaction to the contrast agent. MRI scans are in general well tolerated and do not involve ionising radiation therefore do not carry with them any increased malignancy risk.

Participants will be attending clinic for their routine follow up visits when they complete the assessments and therefore will not need any extra visits to hospital. During their clinic visit they may need to spend slightly more time than they would usually do in order to complete the questionnaires. In order to minimise this we have allowed for carers/family/a member of the study team to assist with the self-reported questionnaires or for the patient to take the questionnaire home with them to complete and post back to the study team.

The participant’s GP will be informed of their involvement within the study. If there are concerns from the answers to the questionnaires that the participants may be at risk of harm to themselves or to others then this will be discussed with the participant's GP or other teams. The participants will be aware of this. In the unlikely event that any psychological distress is caused to the participants by completing the questionnaires, we would address this within the clinic visit and if necessary refer to their GP or local psychiatric services for further support.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from a REC for the study protocol, informed consent forms and other relevant documents

Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site. All correspondence with the REC will be retained. The Chief investigator will produce the annual reports as required and will notify the REC of the end of the study. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Amendments

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

8.3 Peer review

8.4 Patient & Public Involvement

The study protocol and patient information sheet have been reviewed by the JAFFA panel - a patient and public involvement (PPI) lay research panel based at Brighton and Sussex University Hospitals Trust. Their feedback was instrumental in restructuring the protocol and PIS to make the design of the study clearer to understand and confirm the importance of using quality of life as the primary outcome.

A lay summary of the study was circulated to The Brains Trust PPI panel during the design of the study who again aided in the structure of the study and gave their full support. It was also sent to The Brain Tumour Charity Research Involvement Network, a group of brain tumour patients and their carers. They sent detailed feedback and felt the study was well explained and clear to understand and some points they raised surrounding the sequence of consenting and enrolling in the study led to an a adaptation of the study protocol. They did not feel undergoing and extra MRI scan would be onerous the participants. They unanimously agreed that the objectives of the study were worth pursuing and that it was a valid study question.

8.5 Protocol compliance

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

8.6 Data protection and patient confidentiality

All investigators and study site staff will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

No patient identifiable data will be accessed by anyone outside of their usual direct care team. The study members are all part of the usual direct care team. Patient identifiable data will be accessed by the study team in order to identify eligible participants from the MDM list and if necessary access their postal addresses in order to send them the initial PIS and consent form. All paperwork from the study will be recorded using the participant study ID numbers. Data will be pseudo anonymised locally and survival data will be collected on participants at the end of the study period. The study database created at the end of the study period once survival data has been collected will be fully anonymised. No patient identifiable data will be recorded on the study database. Data protection and confidentiality will be respected at all times. Data will be handled as per data management above.

Prior to MRI scans being transferred electronically via the national IEP system, the scans will be allocated the participants study ID by the local study team. No patient identifiable data will therefore be transferred electronically.

The database will be kept on password protected NHS computers within a locked office. The paper copies of the CRFs will be kept within secure NHS offices by the members of the local study team. Any transfer of data will be done via secure NHS.net e-mail systems or an encrypted USB however no patient identifiable details will be transferred off site.

The data will be stored for 5 years after the end of the study date.

8.7 Indemnity

The study will be covered by the usual NHS indemnity policies

8.8 Access to the final study dataset

All members of the study team will have access to the completed anonymised database if necessary.

8.9 Study & safety assessments

As the study does not employ an Investigational Medicinal Product, Adverse Events (AE) or Serious Adverse Events (SAE) will be recorded and reported as per Sponsor's guidelines (Brighton & Sussex University Hospitals NHS Trust) and Health Research Authority (HRA) (see Figure 2 below).

A serious adverse event (SAE) is defined as an untoward occurrence that:

(a) results in death;

(b) is life-threatening;

(c) requires hospitalisation or prolongation of existing hospitalisation;

(d) results in persistent or significant disability or incapacity;

(e) consists of a congenital anomaly or birth defect; or

(f) is otherwise considered medically significant by the investigator

An SAE occurring to a research participant will be reported to the main REC where in the opinion of the Chief Investigator the event was:

- Related – that is, it resulted from administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

	Who	When	How	To whom
SAE	Chief Investigator (CI) or sponsor	Within 7-14 days of the CI becoming aware of the event (in line with the Sponsor's Collaboration Agreement	SAE report form for non-CTIMPs available from HTA website	Main REC for the trial
Urgent safety measures	Chief Investigator (CI) or sponsor *Or exceptionally by local principal investigator (PI)*	(i) Immediately (ii) Within 3 days	(i) By telephone (ii) Notice in writing setting out the reasons for urgent safety measures and the plan for further action	Main REC for trial REC co-ordinator will acknowledge within 30days *If notified by PI, relevant local REC should also be informed*

9 DISSEMINIATION POLICY

9.1 Dissemination policy

Findings will be submitted for presentation at national and international conferences and publication in peer reviewed journals. Brains Trust will also disseminate the anonymised study findings through their patient support groups and social media. We will share the results of this study with individual participants if they express a desire for them. No patient identifiable data will be published. The final

study data will be owned by the CI. As is current accepted practice, it will be unacceptable for collaborators to independently publish data of individuals that they have recruited for the study

9.2 Authorship eligibility guidelines and any intended use of professional writers

The final study report will be written up by the CI and main protocol contributors. The authorship of the study will include the study teams who will be asked for input to the final study manuscript.

10. APPENDICIES

11.1 Appendix 1- Questionnaires to be used

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