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FUTURE-GB: Functional and ultrasound-guided resection of glioblastoma: assessing the use of additional imaging during surgery to improve outcomes for patients with glioblastoma brain tumours

Submission date	**Recruitment status**	[X] Prospectively registered
07/05/2020	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
14/08/2020	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
06/08/2024	Cancer	[_] Record updated in last year

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-ultrasound-and-diffusion-tensor-imaging-during-surgery-for-glioblastoma-future-gb (added 17/03/2022)

Background and study aims

Glioblastoma (GB) is the most common primary brain tumour and is incurable. It grows very quickly from the brain tissue itself, rather than from a cancer elsewhere in the body. It is expected that the number of people with a brain tumour will rise by 6% in the UK between 2014 and 20351. However, prognosis (outcome) remains extremely poor, with most people surviving just over 12 months, and as a patients tumour grows patients experience a reduction (decline) in their quality of life. Therefore, we need to ensure quality of life, which remains difficult. The main treatments for GB are surgery, radiotherapy and chemotherapy, given in combination.

For patients where it is thought that surgery will benefit, a surgeon often removes as much tumour as possible, whilst limiting the risk of causing damage, such as weakness, speech, or cognitive difficulties. However, which technology a surgeon should use during surgery to remove the tumour safely is unclear. This can affect how soon the cancer returns, what effects of surgery or symptoms a patient develops, and how a patient feels.

High-frequency sound waves that create an image, called Ultrasound (US), is one of the tools a surgeon can use during the operation to find the tumour and see how much is removed. Another technology, Diffusion Tensor Imaging (DTI), allows important nerve pathways involved in certain functions, for example, speech/language, vision and movement, to be avoided in surgery.

This trial aims to see if GB surgery with these extra technologies (tools) added to the standard ones, increases a patient's good functioning quality of life, so-called Deterioration Free Survival (DFS).

Who can participate?
Adults aged 18 - 70 years, with a primary GB tumour which is maximally resectable and are suitable candidates for the treatment under investigation.

What does the study involve?
Participants will be randomly allocated to receive either brain surgery with standard methods without US and DTI, or surgery with the addition of US and DTI as well as standard tools. Patients may not know into which group they have been placed. They will be recruited from at least 15 NHS hospitals that routinely undertake GB surgery and have access to these tools. The trial will result in only minor changes to the present care pathway. After agreeing to take part, participants will be asked to complete questionnaires about their quality of life, such as their walking, ability to look after their personal hygiene, how they feel. They will also have a brief physical and cognitive/functional assessment before their surgery. Afterwards, the questionnaires and assessments will be repeated, before leaving hospital, and at three monthly intervals until 24 months after agreeing to take part (consenting). These will be combined with planned hospital visits. How long a patient lives will also be recorded.

What are the possible benefits and risks of participating?
There may not be any direct benefit to the patient, however, information gathered will benefit future patients. There are no additional risks.

Where is the study run from?
John Radcliffe Hospital (UK)

When is the study starting and how long is it expected to run for?
April 2020 to April 2027

Who is funding the study?
National Institute for Health Research EME Programme (UK)

Who is the main contact?
Melody Chin, futuregb@nds.ox.ac.uk

Contact information

Type(s)
Public

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05399524

Integrated Research Application System (IRAS)
264482

Central Portfolio Management System (CPMS)
45956

National Institute for Health and Care Research (NIHR)
127930

Study information

Scientific Title
Functional and Ultrasound guided Resection of Glioblastoma. A two stage trial. Stage 1 – Non-randomised collaborative learning and evaluation phase of participating centres (IDEAL Stage 2b study), followed by Stage 2 – A Multicentre Phase III trial with 2 mechanistic substudies.

Acronym
FUTURE-GB

Study objectives
This trial aims to see if GB surgery with ultrasound and diffusion tensor imaging added to the standard care, increases a patient's good functioning quality of life, so-called deterioration-free survival (DFS).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 05/10/2020, London - Harrow Research Ethics Committee (Level 3, Block B, Whitefriars,
Lewins Mead, Bristol, BS1 2NT; +44 (0)207 104 8057; harrow.rec@hra.nhs.uk) ref: 20/LO/0840

Study design
Multicentre randomized controlled trial

Primary study design
Interventional

Study type(s)
Quality of life

Health condition(s) or problem(s) studied
Glioblastoma

Interventions

Stage 1 (IDEAL IIB study) of the trial is observational only and all participants will receive all technologies during surgery.
Stage 2 will be randomised. Randomisation will be via the web-based service provided by the Oxford Clinical Trials Research Unit (OCTRU), using the method of minimisation. Participants will be randomised 1:1 to either:
1. Standard care surgery (neuronavigation based on preoperative imaging and intraoperative use of 5-ALA)(Control arm)
2. Standard care surgery (neuronavigation based on preoperative imaging and intraoperative use of 5-ALA) AND of DTI neuronavigation and NiUS (Intervention arm)

At baseline all participants will undergo a routine preoperative neuronavigation MRI scan. Those participants randomised to the experimental arm, will also have a DTI scan (additional 5 minutes in the MRI). All participants will then undergo the planned resection of their tumour, with the additional technologies if they are in the experimental arm. Following surgery, participants in both arms have the same follow up schedule and undergo standard clinical care for a total of 24 months.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Stage 1:
Feasibility of using DTI and NiUS in addition to standard of care for neurosurgery assessed using:
1. Operation length measured using patient records, analysed post-operatively
2. Successful use of the technology measured using operating surgeon theatre reports completed during surgery and analysed post-operatively
3. Tumour resection shown by pre and post-op MRI scan
4. Surgical complications measured using number of return visits to theatre, and other medical complications and analysed at discharge

Stage 2:
Deterioration Free Survival (Global Health Status) measured using a composite measure obtained from the QLQ-C30 patient and proxy questionnaire at baseline, 5 days post-op /discharge, 6 weeks post-op, 3 month post-op, then every 3 months subsequently up to 24 months post-op, Progression-Free Survival (PFS) and Overall Survival (OS) measured using patient records

Updated 05/04/2022:
Deterioration Free Survival (Global Health Status) measured using a composite measure obtained from the QLQ-C30 patient and proxy questionnaire at baseline, 6 weeks post-op, 3 months post-op, then every 3 months subsequently up to 24 months post-op, Progression-Free Survival (PFS) and Overall Survival (OS) measured using patient records

Key secondary outcome(s)
Current secondary outcome measures as of 19/08/2022:

Secondary Outcomes (In Stage 2 only)
1. To assess whether additional intraoperative imaging (DTI and iUS*) to standard of care (Neuronavigation and intraoperative 5-ALA) improves DFS where deterioration relates to physical functioning, social functioning from the QLQ-C30, and motor dysfunction and communication deficit. Measured using 4 composites using the respective domain of QLQ-C30

(physical functioning and social functioning) and BN20 (motor dysfunction and communication deficit) combined with PFS and OS. To be recorded at baseline; 6wks post-op., 3mths post-op., and then 3mthly up to 24 months
2. To assess whether additional intraoperative imaging (DTI and iUS*) to standard of care (Neuronavigation and intraoperative 5-ALA) improves time to deterioration. Measured similarly to DFS with the exception that progression is excluded as an event (i.e. only deterioration or death are considered). There will be five time to deterioration outcomes, one for each of the domains utilised in the primary and secondary DFS outcomes, used in turn to define deterioration. To be recorded at 6wks post-op., 3mths post-op., and then 3mthly up to 24 months
3. To assess whether additional intraoperative imaging (DTI and IUS*) to standard of care (Neuronavigation and intraoperative 5-ALA) improves Overall Survival (OS). Measured by OS (time from randomisation to death or trial closure). To be recorded at 24 months
4. To assess whether additional intraoperative imaging (DTI and iUS*) to standard of care (Neuronavigation and intraoperative 5-ALA) improves Progression Free Survival (PFS). Measured by PFS (time from randomisation to radiological tumour progression on imaging, as agreed in local MDT). To be recorded from MRI at 6 months post-op., and then 3mthly up to 24 months
5. To assess whether additional intraoperative imaging (DTI and iUS*) to standard of care (Neuronavigation and intraoperative 5-ALA) improves the extent of tumour resection. Measured by extent of resection as % of pre-operative tumour volume on postoperative contrast enhanced MRI. To be recorded at post-operative review
6. To assess whether additional intraoperative imaging (DTI and iUS*) to standard of care (Neuronavigation and intraoperative 5-ALA) improves the incidence of surgical complications. Measured by number and type of surgical complications. To be recorded at 5 days post-op, or discharge date (whichever is soonest); 6wks post-op., 3mths post-op., and then 3mthly up to 24 months
7. To assess whether additional intraoperative imaging (DTI and iUS*) to standard of care (Neuronavigation and intraoperative 5-ALA) improves the number of patients eligible for adjuvant treatment following surgery. Measured by number of patients eligible for adjuvant treatment at 3mths post-op.
8. To assess whether additional intraoperative imaging (DTI and iUS*) to standard of care (Neuronavigation and intraoperative 5-ALA) improves functional outcome postoperatively. Measured by WHO performance status, mini-MoCA (Montreal Version), Barthel Index, and MRC grading of power in all 4 limbs. To be recorded at baseline, 5 days post-op., or discharge date (whichever is soonest); 6wks postop., 3mths post-op., and then 3mthly up to 24 months (MRC grading to be assessed at baseline and 5 days post-op., or discharge date only)
9. Assess the correlation of proxy to participant classification assessment of quality of life. Measured by answers to questions 29 and 30 of the QLQ-C30. Ideally answers will be provided to all of the QLQ-C30 and BN20. To be recorded at baseline, 6wks post-op., 3mths post-op., and then 3mthly up to 24 months. Proxy will not complete questionnaires when participant stops completing them.

Tertiary Mechanistic Study Objectives (in Stage 2 and on a sub set of participants only)
1. To assess the sensitivity and specificity of the anatomico-spatial location of DTI fibre tracts compared with intraoperative direct electrical stimulation/behavioural change without stimulation but related to adjacent white fibre tract in patients undergoing awake surgery, or motor evoked potential changes in patients undergoing surgery. Measured by sensitivity and specificity calculation using pre- and post-surgery MRI images. Analysis will be undertaken post-surgery.
2. To assess the sensitivity and specificity of iUS* to identify the tumour boundary when compared with 5-ALA, navigated biopsies will be taken from tumour boundary tissue planned for

resection. Measured by intra operative iUS* images and post-operative MRI scans and intraoperative biopsy sample. Analysis will be undertaken post-surgery when biopsy results are available.

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Previous secondary outcome measures:

Measured at baseline, 5 days post-op/discharge, 6 weeks post-op, 3 month post-op, then every 3 months subsequently up to 24 months post-op (unless otherwise mentioned):
1. Physical functioning, social functioning measured using the QLQ-C30
2. Motor dysfunction and communication deficit measured using the QLQ-BN20
3. Time to deterioration measured using a composite measure obtained from the QLQ-C30 patient and proxy questionnaire, progression-free survival (PFS) and overall survival (OS) measured using patient records
4. Progression Free Survival (PFS) measured as time from randomisation to radiological tumour progression on imaging
5. Extent of tumour resection measured as % of pre-operative tumour volume on postoperative contrast enhanced MRI at post-op review
6. Incidence of Surgical Complications measured using patient records
7. Number of patients eligible for adjuvant treatment (for radiotherapy and/or chemotherapy) following surgery measured using patient records
8. Functional Outcome measured by results from standardised assessments:
8.1. Activity ability measured using WHO performance status
8.2. Cognitive function measured using Montreal Cognitive Assessment (MOCA)
8.3. Performance in activities of daily living measured using the Barthel Index
8.4. Muscle power measured using MRC grading of power in all 4 limbs
9. Participant classification assessment of quality of life, measured by answers to QoL questions provided by the participant and their proxy

Stage 2 tertiary outcome measures:
1. Location of nerve tracts measured using DTI imaging pre and post-surgery
2. Location of nerve tracts measured using intraoperative direct electrical stimulation or motor evoked potential changes during surgery
3. Location of tumour boundary measured using intraoperative NiUS images
4. Location of tumour boundary measured using post-operative MRI scans
5. Location of tumour boundary measured using intraoperative biopsy samples

Completion date
30/04/2027

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 05/04/2022:
1. Aged 18 - 70 years
2. Neuro-oncology Multi-Disciplinary Team (MDT) decision that the imaging shows a primary GB tumour which is maximally resectable (attempted gross total resection of all enhancing tumour)
3. Patient is suitable for concomitant 6 weeks adjuvant radiotherapy and temozolomide (TMZ) chemotherapy or adjuvant TMZ at the time of MDT decision
4. Able to receive 5-ALA

5. Willing and able to give informed consent
6. Able to complete trial questionnaires, this may be with support where English is not their first language (where compatible with the validation of questionnaires). (Stage 2 only)
7. Able to provide a proxy who is willing to complete questionnaires as requested (Stage 2 only)

Previous inclusion criteria from 23/09/2021 to 05/04/2022:
1. Aged 18 - 70 years
2. Neuro-oncology Multi-Disciplinary Team (MDT) decision that the imaging shows a primary GB tumour which is maximally resectable (attempted gross total resection of all enhancing tumour)
3. Patient is suitable for concomitant 6 weeks adjuvant radiotherapy and temozolamide (TMZ) chemotherapy or adjuvant TMZ at the time of MDT decision
4. Willing and able to give informed consent
5. Able to understand written English to enable completion of trial questionnaires
6. Able to provide a proxy who is willing to complete questionnaires as requested

Original inclusion criteria:
1. Aged 18 - 75 years
2. Neuro-oncology Multi-Disciplinary Team (MDT) decision that the imaging shows a primary GB tumour which is maximally resectable (attempted gross total resection of all enhancing tumour)
3. Patient is suitable for concomitant 6 weeks adjuvant radiotherapy and temozolamide (TMZ) chemotherapy or adjuvant TMZ at the time of MDT decision
4. Willing and able to give informed consent
5. Able to understand written English to enable completion of trial questionnaires
6. Able to provide a proxy who is willing to complete questionnaires as requested

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
70 years

Sex
All

Key exclusion criteria
1. Midline/basal ganglia/cerebellum/brainstem GB
2. Multifocal GB
3. Recurrent GB
4. Suspected secondary GB
5. Contraindication to MRI

Date of first enrolment

18/12/2020

Date of final enrolment
30/04/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
John Radcliffe Hospital
Oxford University Hospitals NHS Trust
Headley Way
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United Kingdom
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Study participating centre
Southmead Hospital
Southmead Rd
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Study participating centre
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51 Little France Crescent
Old Dalkeith Rd
Edinburgh
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Study participating centre
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James Cook University Hospital
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Study participating centre
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South West Neurosurgery Centre
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Study participating centre
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Study participating centre
The Royal Victoria Infirmary
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Study participating centre
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South Wharf Road
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Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research EME Programme

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The anonymised master data set generated by this study will be held as per local CTU policies. It will be available on request from futuregb@nds.ox.ac.uk after the final results publication.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		15/11/2022	23/11/2022	Yes	No
HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes