Study Title: **FUTURE-GB – Functional and Ultrasound guided Resection of Glioblastoma.**

A two Stage trial.

Stage 1 – Non-randomised learning evaluation of participating centres (an IDEAL study), followed by Stage 2 – A multi-centre randomised trial with 2 mechanistic sub-studies.

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Chief Investigator: Professor Puneet Plaha, Nuffield Department of Surgical Sciences, University of Oxford

Co-Chief Investigators: Ms Sophie Camp, Imperial College Healthcare NHS Trust

Professor Dipankar Nandi, Imperial College Healthcare NHS Trust

Investigators:	Professor Jonathan Cook, Oxford Clinical Trials Research Unit, University of Oxford
	Professor Adrian Lim, Imperial College Healthcare NHS Trust
	Professor Martin Taphoorn, Haaglanden Medical Center, University of Leiden, Netherlands
	Professor Linda Driven, Haaglanden Medical Center, University of Leiden, Netherlands.
	Professor Peter McCulloch, Nuffield Department of Surgical Sciences, University of Oxford
	Professor Natalie Voets, Nuffield Department of Surgical Sciences, University of Oxford
	Dr Matthew Grech-Sollars, Imperial College Healthcare NHS Trust
	Professor Colin Watts, University of Birmingham
	Dr Helen Bulbeck, Brainstrust
	Professor Michael Jenkinson, University of Liverpool & The Walton Centre
	Dr Matt Williams, Imperial College Healthcare NHS Trust
	Professor Colin Watts, University Hospitals Birmingham Foundation NHS Trust
Sponsor:	University of Oxford
	Joint Research Office, 1st Floor, Boundary Brook House, Churchill Drive, Headington, OX3 7GB
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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY CONTACTS

Chief Investigator	**Professor Puneet Plaha** Consultant Neurosurgeon Associate Professor Nuffield Department of Surgical Sciences, University of Oxford Level 3, West Wing, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU	
Co-Chief Investigators	**Miss Sophie Camp** Consultant Neurosurgeon Imperial College HealthCare NHS Trust Fulham Palace Road, Hammersmith, London W6 8RF **Professor Dipankar Nandi** Consultant Neurosurgeon Imperial College HealthCare NHS Trust Fulham Palace Road, Hammersmith, London W6 8RF	
Sponsor	University of Oxford Joint Research Office, 1st Floor, Boundary Brook House, Churchill Drive, Headington, OX3 7GB	
Funder(s)	National Institute for Health Research Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership	
Clinical Trials Unit	Oxford Clinical Trials Research Unit (OCTRU) University of Oxford Botnar Research Centre, Windmill Road, Headington, Oxford OX3 7LF	
Statistician	**Ariel Wang** University Lecturer in Statistics Oxford Clinical Trials Research Unit, University of Oxford Botnar Research Centre, Windmill Road, Headington, Oxford OX3 7LF	
Committees	TRIAL STEERING COMMITTEE (TSC) Chair: **Mr Philip Weir** Consultant Neurosurgeon Belfast Trust	DATA SAFETY AND MONITORING COMMITTEE (DSMC) Chair: **Mr Ian Sabin** Consultant Neurosurgeon Wellington Hospital, London

2. LAY SUMMARY

2.1. Aims and Background

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 2035[1]. However, prognosis (outcome) remains extremely poor, with most people surviving just over 12 months, and as a patient's 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).

2.2. Design

FUTURE-GB is a two Stage trial.

Stage 1 a non-randomised cohort study using the IDEAL Stage 2b design format[2] . It will evaluate standard care surgery with the addition of DTI imaging and the ultrasound imaging during the operation. This Stage will ensure standardisation of the use of the technologies across all trial centres by expert mentoring, and will evaluate quality of delivery, including monitoring of the learning curve for the group as a whole.

Stage 2 is a randomised controlled trial. This means those who agree to take part will be allocated by chance (like the tossing of a coin). The trial plans to enrol 357 newly diagnosed patients 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 will not know into which group they have been placed, nor will the research team assessing them before and after surgery. 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.

2.3. Public and Patient Involvement

The trial focuses on keeping good quality of life for people living with a GB for as long as possible. It has been designed with the help of patient support groups at the Brain Tumour Charity and Brainstrust, the Patient Relative Advisory Group at the Oxford University Hospitals NHS Foundation Trust and the Brain Tumour PPI Group at Imperial College Healthcare NHS Trust. Dr Helen Bulbeck (Brainstrust's Director) has been part of the trial proposal and is one of the trial's investigators.

2.4. Dissemination:

Trial results will be published and widely shared via a variety of channels. If this trial shows that patients benefit, it is expected that the tools will become standard care and help GB patients in all 24 UK NHS neurosurgery units, and worldwide.

3. SYNOPSIS

Study Title	FUTURE-GB – Functional and Ultrasound guided Resection of GlioBlastoma (GB): A two-Stage trial. Stage 1: non-randomised learning Stage evaluation of participating centres (an IDEAL study). Stage 2: a multicentre definitive trial with 2 mechanistic sub-studies.
Internal ref. no. / short title	FUTURE-GB
Study registration	ISRCTN: 38834571
Sponsor	University of Oxford
Funder	NIHR EME Programme
Study Design	FUTURE-GB is a 2-Stage trial: Stage 1 is a non-randomised multicentre learning and evaluation Stage (IDEAL IIB study), and Stage 2 a prospective, multicentre definitive randomised controlled trial.
Study Participants	Newly diagnosed glioblastoma (GB) patients
Sample Size	Up to 75 patients will participate in Stage 1, (up to 5 per centre). 357 patients will participate in the Stage 2, randomised controlled trial
Planned Study Period	Patients participating in the trial will be followed at 3 monthly intervals up to 24 months after randomisation.
Planned Recruitment period	6-9 months Stage 1 and then 27 months for Stage 2.
Intervention(s)	Surgery to resect the GB using Diffusion Tensor Imaging (DTI) and Navigated intraoperative Ultrasound (NiUS) (where available) in addition to standard care (i.e. neuronavigation based on preoperative MRI and intraoperative use of 5-aminolevulinic acid)
Comparator	The comparator is standard care as per current NICE guidelines (i.e. neuronavigation based on preoperative MRI and intraoperative use of 5-aminolevulinic acid).

Stage 1	Objectives	Outcome Measures	Timepoint(s)
Primary Outcomes	To demonstrate the feasibility of using DTI and NiUS in addition to standard of care (neuronavigation based on preoperative MRI and intraoperative use of 5-ALA) for neurosurgery (at selected UK NHS hospitals).	1. Operation length 2. Successful use of DTI neuronavigation and frequency and duration of NiUS use to achieve complete tumour resection without major neurological deficit 3. Extent of tumour resection assessed on postoperative MRI scan. 4. Surgical Complication and Serious Adverse Events	Hospital discharge

Stage 2	Objectives	Outcome Measures	Timepoint(s)
Primary Outcomes	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (neuronavigation based on preoperative MRI scan and intraoperative 5-ALA) improves Deterioration Free Survival (DFS) (Where deterioration relates to global health status only)	Composite of global health status domain of the QLQ-30 questionnaire, Progression Free Survival (PFS) and Overall Survival (OS) with an event defined as either deterioration, progression or death.	To be recorded at baseline; 5 days post-op., or discharge date (whichever is soonest); 6wks post-op., 3mths post-op., and then 3mthly up to 24 months
Secondary Outcomes	To assess whether additional intraoperative imaging (DTI and NiUS) 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	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; 5 days post-op., or discharge date (whichever is soonest); 6wks post-op., 3mths post-op., and then 3mthly up to 24 months

Stage 2	Objectives	Outcome Measures	Timepoint(s)
Secondary Outcomes	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (Neuronavigation and intraoperative 5-ALA) improves time to deterioration	Defined similar 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 utilized utilised in the primary and secondary DFS outcomes, used in turn to define deterioration.	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
Secondary Outcomes	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (Neuronavigation and intraoperative 5-ALA) improves Overall Survival (OS)	OS (time from diagnosis to death or trial closure)	To be recorded at 24 months
Secondary Outcomes	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (Neuronavigation and intraoperative 5-ALA) improves Progression Free Survival (PFS)	PFS (time from diagnosis to radiological tumour progression on imaging, as agreed in local MDT	MRI at 6 months post-op., and then 3mthly up to 24 months or an MRI performed outside protocol if patient is symptomatic
Secondary Outcomes	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (Neuronavigation and intraoperative 5-ALA) improves the Extent of tumour resection	Extent of resection as % of pre-operative tumour volume on postoperative contrast enhanced MRI	Post-operative review
Secondary Outcomes	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (Neuronavigation and intraoperative 5-ALA) improves the incidence of surgical complications	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

Stage 2	Objectives	Outcome Measures	Timepoint(s)
Secondary Outcomes	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (Neuronavigation and intraoperative 5-ALA) improves the number of patients eligible for adjuvant treatment following surgery	Number of patients eligible for adjuvant treatment	3mths post-op.
Secondary Outcomes	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (Neuronavigation and intraoperative 5-ALA) improves functional outcome postoperatively	WHO performance status MOCA Barthel Index MRC grading of power in all 4 limbs	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
Secondary Outcomes	Assess the correlation of proxy to participant classification assessment of quality of life	At a minimum, answers to questions 29 and 30 of the QLQ-C3. Ideally answers will be provided to all of the QLQ-C30 and BN20.	Baseline, 5 days post-op., or discharge date (whichever is soonest); 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 – on a sub set of participants –	To assess the sensitivity and specificity of the anatomico-spatial location of DTI fibre tracts compared with intraoperative direct electrical stimulation in patients undergoing awake surgery	Sensitivity and specificity calculation using pre and post-surgery MRI images	Analysis will be undertaken post-surgery.
Tertiary Mechanistic Study Objectives – on a sub set of participants –	To assess the sensitivity and specificity of NiUS to identify the tumour boundary when compared with 5-ALA, navigated biopsies will be taken from tumour boundary tissue planned for resection.	Intra operative NiUS images and post-operative MRI scans and Intraoperative biopsy samples	Analysis will be undertaken post-surgery when biopsy results are available.

4. ABBREVIATIONS

5-ALA	5-AminoLevulinic Acid – also known as the Pink Drink
CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
DFS	Deterioration Free Survival
DSMC	Data Safety Monitoring Committee
DTI	Diffusion Tensor Imaging
EORTC	European Organisation for Research and Treatment of Cancer
FUTURE-GB	FUncTional and Ultrasound guided Rsection of GlioBlastoma
GB	Glioblastoma
GCP	Good Clinical Practice
GP	General Practitioner
GTR	Gross Total Resection
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
ICF	Informed Consent Form
IDEAL	Idea, Development, Exploration, Assessment, Long-term study
ITT	Intention To Treat
iUS	Intraoperative Ultrasound
MDT	Multi Disciplinary Team
MHz	Megahertz
mm	millimetre
MOCA	The Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NiUS	Navigated Intraoperative Ultrasound
OS	Overall Survival
PFS	Progression Free Survival

PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PP	Protocol Population
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure
QLQ	Quality of Life Questionnaire
QLQ-BN20	Quality of Life Questionnaire Brain
QLQ-C30	Quality of Life Questionnaire Cancer
QoL	Quality of Life
TMZ	Temozolomide
TSC	Trial Steering Committee
US	Ultrasound
WHO	World Health Organisation

5. BACKGROUND AND RATIONALE

5.1. Health problem to be addressed

Glioblastoma (GB) is a cancer with unmet needs.

GB is the most frequent and aggressive form of brain cancer, with an incidence of 4.64/100,000/year in the UK.[3] Prognosis remains extremely poor with median survival just over 12 months[4] and as the tumour grows patients experience a progressive decline in health-related quality of life (HRQoL), and caregivers report high levels of distress and carer burden.[5] Resistance to treatment leads to poor survival,[6] with high costs to the patient, relatives, society, and the economy.[6-8]

Although primary brain tumours represent only 3% of all cancers, a brain tumour reduces life expectancy by an average of 20 years, the highest of any cancer, and accounts for more average years of life lost than any other cancer.[6-8] GB affects adults in their economic prime, and is a leading cause of death in those under 40 years, costing the economy £578M per year.[6-8] To date, there has been little progress in improving outcome, with many trials failing to show an effect.[9] Furthermore, the Department of Health and Cancer Research UK have identified research in this field as being under resourced,[10] and recently allocated additional funding of £45 million.[11] The Brain Tumour Charity have also recently invested £2.8M into the Tessa Jowell BRAIN-MATRIX (British feasibility study of molecular stratification and targeted therapy to optimise the clinical management of patients with glioma by enhancing clinical outcomes, reducing avoidable toxicity, improving management of post-operative residual and recurrent disease and improving survivorship), a trial aimed at radically increasing opportunities for brain tumour

patients to access non-standard treatments.[12] This is timely, as the incidence of brain tumours is projected to rise by 6% in the UK between 2014 and 2035.[1]

A recent James Lind Alliance Priority Setting Partnership[13] revealed two of the top ten priorities in Neuro-oncology are concerned with the long-term physical and cognitive effects of treatment, and the impact of extent of resection on survival. These themes are reflected in the comments from engagement with the Neuro-oncology Patient and Public Involvement (PPI) Groups at Imperial College Healthcare NHS Trust and Oxford University Hospitals NHS Foundation Trust, the Brainstrust PPI group and the Brain Tumour Charity-Research Involvement Network (BTC-RIN). It is apparent that extending survival without functional compromise, and maintaining HRQoL is optimum for patients and relatives, given GB is an incurable cancer with extremely short survival.

5.2. Health Related Quality of Life (HRQoL)

Health Related Quality of Life (HRQoL) is important for patients as GB is incurable and median survival is short. Of late, the role of Quality of Life (QoL) measurement has become increasingly important in oncology trials. HRQoL is a key outcome of interest to patients, and more recently has been used as a secondary outcome measure in a number of randomised trials of GB treatment.[14] For a patient with GB, QoL is particularly significant, given there is substantial potential for a negative impact on HRQoL due to surgical resection, as well as deterioration due to disease progression. Therefore, it is critical that assessments of QoL are relevant to the patient population and the effect of their condition. The EORTC QLQ-C30 has been widely used in oncology trials for over 20 years (currently version 3), to assess the quality of life of cancer patients.[15,16] More recently, an additional brain cancer specific module (QLQ BN-20) has been produced which complements the main QLQ-C30, with more brain cancer specific symptoms and additional QoL domains to ensure a comprehensive and relevant assessment for these patients.[17]

In newly diagnosed GB, QoL may be relatively high, close to that of a healthy population, it can however deteriorate rapidly. The ultimate aim of treatment, therefore, is to prolong survival in a way that is clinically meaningful to the patient, i.e. whilst maintaining their reported HRQoL at as high a level as possible. Accordingly, in the FUTURE-GB trial the primary outcome is the patient centric Deterioration Free Survival (DFS),[18] which takes into account decline in QoL, as well as survival, and disease progression.

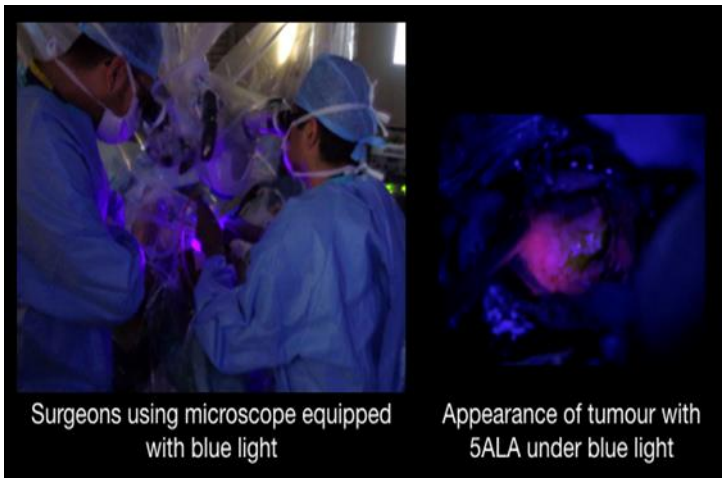
5.3. Knowledge Gap

There is currently a knowledge gap: surgery is the mainstay of treatment for GB but optimum surgical technologies remain unclear. Surgery to resect GB is integral to maximum first line treatment, with a greater impact on survival than non-operative treatments (radiotherapy and chemotherapy).[19] It improves symptom control, reduces dependence on dexamethasone, and increases progression free and overall survival.[20,21] However, maximising the extent of surgical resection must be balanced against the potential risk of causing neurological deficit. It remains unclear which technologies should be employed intraoperatively, without increasing physical and/or cognitive dysfunction. A recent Cochrane review emphasized the lack of high-quality evidence to support the use of any specific intraoperative imaging technology.[22] Research regarding which technologies have the greatest efficacy is of poor quality, with few details concerning the impact of more radical surgical resection on neurological function. Furthermore, there are no ongoing or new trials evaluating Navigated intraoperative UltraSound (NiUS),

Diffusion Tensor Imaging (DTI), or 5-aminolevulinc acid (5-ALA), that will influence treatment guidelines and policy.

5.4. Current surgical standard of care

The current standard of care advises gross total resection (GTR), i.e. removing all enhancing tumour seen on the preoperative MRI scan), where appropriate, using neuronavigation, based on a preoperative MRI scan, and intraoperative 5-aminolevulinic acid (5-ALA), which is an oral solution administered prior to surgery to facilitate tumour visualisation and differentiation from surrounding normal brain tissue during surgery.[5] However there is wide variations of surgical standard of care across the UK. Neuronavigation systems allow the craniotomy to be placed accurately, and the surgeon to locate the tumour. However, once the dura has been open, cerebrospinal fluid (CSF) and/or cyst fluid is drained, and, as tumour is removed, a phenomenon known as 'brain shift occurs',[23] rendering standard neuronavigation inaccurate when identifying the tumour margins. Consequently, a surgeon may halt the resection at what is perceived to be tumour margin, inadvertently leaving residual disease. 5-ALA use increases the extent of tumour resection and progression free survival (PFS).[20,24] However, 5-ALA only identifies fluorescing tumour immediately apparent in the surrounding tissue, without consideration of volume, or of tumour hidden due to an irregular resection cavity. Furthermore, it does not inform of tissue function.



A survey of all 24 adult UK neurosurgical centres (Telephone and Email survey conducted in 2018 by Oxford), showed wide variation in the use of technologies employed during GB resection. Whilst all centres employ standard neuronavigation and 5-ALA, only 75% have access to iUS, 62% to DTI, and 16% to an intraoperative MRI scanner. However, most of these technologies are not regularly used for tumour resection, with surgeons unclear of the efficacy of each, and what is the optimum combination. Indeed, the National Institute for Health and Care Excellence (NICE) guidance[5] has suggested that the available range of intraoperative technologies are considered, as appropriate, in addition to standard techniques, for tumour resection.

5.5. Combined NiUS and DTI may improve outcome

The desire to achieve a safe, maximal resection, particularly in eloquent regions, has led to an increase in the popularity of intraoperative imaging. This attempts to eliminate the error produced by brain shift, an inherent problem in navigation systems based on preoperative imaging,[23] to demonstrate residual tumour at operation, and to visualise accurately relevant white matter tracts and tumour margins. Two technologies which facilitate surgical resection intraoperatively are NiUS and DTI.

1. NiUS accommodates for brain shift as it is linked to neuronavigation systems and allows the surgeon to track tumour resection in real time. It permits multiple, real time image acquisitions, and at each stage, comparison with the preoperative MRI navigation sequence, to evaluate brain shift and residual disease. NiUS minimally augments operative time,[25] allowing precise

visualization of tumour resection. It is user friendly, widely available, and a pragmatic and cost-effective alternative to intraoperative MRI, which is prohibitively expensive for many UK units. Intraoperative ultrasound, and more recently NiUS, has a long history in brain tumour surgery,[26] facilitating/extending resection,[27-31] and improving survival.[32] It has also been evaluated with respect to histology.[33,34] However, there is a learning curve, and image interpretation, especially once resecting, can be challenging.[26] NiUS demonstrates residual tumour in real time. Indeed, it has been reported that NiUS and 5-ALA provide different information of tumour extent, and when combined, enhance extent of resection.[35] Despite this, there are no randomised trials assessing its efficacy.

2. DTI is a special magnetic resonance imaging (MRI) technique that can identify the location of white matter nerve tracts important for speech/language/visual/motor functions. The location of white matter fibre pathways is the most frequent reason why surgery is halted early, to avoid compromising patient function.[36] DTI is the only method available to visualise functionally important white matter tracts in the vicinity of a tumour before surgery, and can be fused with standard intraoperative navigation systems to enable visualisation of the spatial location of the tracts during surgery, allowing removal of tumour in close proximity. DTI's usefulness in brain tumour surgery has recently been reviewed.[36] Intraoperative visualisation of DTI is reported to contribute to maximising safe resection,[37-39] reducing visual field deficits,[40] and predicting longterm language problems after surgery.[41] A single centre, DTI randomised control trial showed significantly better gross total resection rates, a lower risk of movement loss, and improved life expectancy.[42] Furthermore, DTI-informed awake surgery reduced the occurrence and severity of behavioural problems postoperatively, leading to faster recovery, and shorter hospital stay[43] DTI requires the collection of additional MRI data, specialist software for analysis, and detailed knowledge of white matter anatomy and function. In addition, tract visualisation may be limited where there is peritumoural oedema. As a result, there is only limited data available on the sensitivity and specificity of DTI in GB surgery, particularly with reference to its value as an intraoperative tool and in predicting DFS.

5.5. Pilot data shows that combining techniques is the way forward

Whilst the current aim for GB surgery is resection of all the contrast-enhancing tumour, several small, single centre studies have reported that extending tumour resection beyond the contrast enhanced margin, i.e. suptratotal resection, can increase overall survival without additional disability.[44-46] A recent pilot study,[47] incorporating DTI neuronavigation, 5-ALA guidance, and, where indicated, awake surgery has shown that supratotal resection prolongs Progression Free Survival (PFS). Furthermore, preliminary data in 80 patients, using DTI neuronavigation, in addition to 5-ALA guided surgery, achieved complete tumour resection in 72% of cases (65% using 5-ALA alone), with 3% postoperative disability (5-10% reported in the literature).[48] In 15% of cases the residual tumour on the postoperative MRI scan was "hidden/missed" during surgery and would possibly have been detected using NiUS.

5.6. The need for the FUTURE-GB trial

Surgery to maximally remove tumour is the initial and most important step of the patient pathway for GB patients, and despite the current standard of care,[5] there remains great scope for surgical trials and improvement in outcome.[47] Together with the implementation of the revised brain tumour

classification,[49] which permits more accurate patient categorisation, further enhancing surgical techniques will facilitate additional potential gain for patients.

Intraoperative tools which provide information of residual disease and function are invaluable. Combining intraoperative techniques enhances the extent of resection.[35,47] With the use of NiUS to identify residual disease in real time, and the functional information provided by DTI, in addition to standard care, it is anticipated that these two surgical techniques will prolong GB survival without increasing disability, and whilst maintaining a good quality of life. Increased survival without functional compromise has obvious benefit for patients and relatives, substantial health gains for society, and significant economic implications. Proven intraoperative techniques would be applied as standard care across the NHS, in all 24 hospitals performing adult neurosurgery. In addition, such surgical technologies have clear global appeal and worldwide impact.

However, considering that this wide use of technologies inevitably varies amongst surgeons, major technical variations and significant deficits in competence or experience with trial procedures can compromise Randomised Controlled Trials (RCTs) by increasing "noise", and introducing performance bias in relation to the new method/tool. Therefore, this trial has adopted an initial IDEAL IIB study format,[50,51] a prospective non-randomised multicentre learning and harmonisation stage in which quality control measures and mentoring will be employed prior to the definitive randomised controlled stage of the trial.

6. OBJECTIVES AND OUTCOME MEASURES

6.1. PRIMARY OUTCOME MEASURES

6.1.1. Stage 1

The IDEAL study will determine whether surgeons using the technologies employed in the randomised controlled trial demonstrate acceptable expertise in delivering the new approach prior to proceeding with the randomisation stage.
Note: There are no set levels for acceptable expertise – this will be an evolving process. Factors used to evaluate expertise will include operation length, successful use of DTI neuronavigation, frequency and duration of NiUS use to achieve complete tumour resection without major neurological deficit; and extent of tumour resection.

6.1.2. Stage 2

The primary outcome is Deterioration Free Survival (DFS)[18] using only the global health domain to indicate whether or not deterioration has occurred. Specifically, DFS is defined as the time to a 10-point deterioration from baseline in the global health status domain of the QLQ-C30 version 3 scores (regarded as clinically meaningful)[53], without subsequent 10-point improvement in scores compared with baseline; or progressive disease (radiological tumour progression assessed from scan); or death in the absence of previous definitive deterioration.

The other four domains will be used to define corresponding DFS secondary outcomes.
Note: It is imperative that the primary outcome measure is completed by those participating in the trial, therefore in addition to the participant completing the questionnaires as far as possible, a proxy will be asked to complete a separate set of questionnaires throughout the length of the trial. A record will be

taken of whether participants or proxies or both have completed each of the questionnaires at each data point.

6.2. Secondary Outcome Measures – Stage 2 only

- DFS as defined for the primary outcome except that physical functioning, social functioning from the QLQ-C30, and motor dysfunction and communication deficit from the QLQ-BN20 are each used instead of global health status to determine deterioration.

  Note: The QLQ-C30[15,16] and QLQ-BN20[17] will be collected for participants throughout the follow-up period. The 5 HRQoL scale scores from these two questionnaires which are most pertinent to patients with GB are global health status, physical functioning, social functioning from the QLQ-C30, and motor dysfunction and communication deficit from the QLQ-BN20. Both the QLQ-C30 and the QLQ-BN20 questionnaires will be scored according to the EORTC scoring manual[15] following the strategy employed in the placebo arm of the AVAglio trial.[18]

- Time to Deterioration – defined similar to DFS with the exception that progressive disease is excluded as an event.
  Note: There will be five time to deterioration outcomes, one for each of the scales utilised in the primary and secondary outcome DFS, used in turn to define deterioration.

- Overall Survival (OS) – defined as time from diagnosis to death or trial closure.

- Progression Free Survival (PFS) – defined as time from diagnosis to radiological tumour progression (scan date), as identified by local neuro-oncology MDT agreement.
  Note: Each MDT will investigate as per local protocols to differentiate true versus pseudo progression. Scan date confirming progression will be used as date of progression.

- Extent of tumour resection on postoperative contrast enhanced MRI – measured as a % of the tumour volume when compared to the preoperative MRI scan.

- Surgical complications and serious adverse events – recorded postoperatively and at follow up visits.

- Number of patients eligible for adjuvant treatment following surgery (radiotherapy and/or chemotherapy).

- Functional outcome postoperatively: World Health Organisation (WHO) performance status,[55] MOCA,[56] Barthel Index[57] and MRC power grading in all 4 limbs.

Mechanistic component outcomes:

- Sensitivity and specificity of the anatomico-spatial location of DTI fibre tracts compared with intraoperative direct electrical stimulation in patients undergoing awake surgery.

- Sensitivity and specificity of NiUS to identify the tumour boundary when compared with 5-ALA, navigated biopsies will be taken from tumour boundary tissue planned for resection.

	Objectives	Outcome Measures	Timepoint(s)
Primary Stage 2	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (neuronavigation based on preoperative MRI scan and intraoperative 5-ALA) improves Deterioration Free Survival (DFS) (Where deterioration relates to global health status only)	Composite of global health status domain of the QLQ-30 questionnaire, Progression Free Survival (PFS) and Overall Survival (OS) with an event defined as either deterioration, progression or death.	Baseline; 5 days post-op., or discharge date (whichever is soonest); 6wks post-op., 3mths post op., and then 3mthly up to 24 months
Secondary	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (neuronavigation based on preoperative MRI scan and intraoperative 5-ALA) improves DFS where deterioration relates to physical functioning, social functioning from the QLQ-C30, and motor dysfunction and communication deficit	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.	Baseline; 5 days post-op., or discharge date (whichever is soonest); 6wks post-op., 3mths post op., and then 3mthly up to 24 months
Secondary	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (neuronavigation based on preoperative MRI scan and intraoperative 5-ALA) improves time to deterioration	Defined similar 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 utilized utilised in the primary and secondary DFS outcomes, used in turn to define deterioration.	5 days post-op., or discharge date (whichever is soonest); 6wks post-op., 3mths post op., and then 3mthly up to 24 months
Secondary	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (neuronavigation based on preoperative MRI scan and intraoperative 5-ALA improves Overall Survival (OS)	OS (time from diagnosis to death or trial closure)	24 months

	Objectives	Outcome Measures	Timepoint(s)
Secondary	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (neuronavigation based on preoperative MRI scan and intraoperative 5-ALA) improves Progression Free Survival (PFS)	PFS (time from diagnosis to radiological tumour progression on imaging, as agreed in local MDT).	MRI at 6 months post-surgery and then 3mthly up to 24 months or an MRI performed outside protocol if patient is symptomatic.
Secondary	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (neuronavigation based on preoperative MRI scan and intraoperative 5-ALA) improves the Extent of tumour resection	extent of resection as % of pre-operative tumour volume on postoperative contrast enhanced MRI	Post-operative review
Secondary	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (neuronavigation based on preoperative MRI scan and intraoperative 5-ALA) improves the incidence of surgical complications	number and type of surgical complications	3mths post-op.
Secondary	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (neuronavigation based on preoperative MRI scan and intraoperative 5-ALA) improves the number of patients eligible for adjuvant treatment following surgery	number of patients eligible for adjuvant treatment	5 days post-op., or discharge date (whichever is soonest); 6wks post-op.,3mths post op., and then 3mthly up to 24 months
Secondary	To assess whether additional intraoperative imaging (DTI and NiUS) to standard of care (neuronavigation based on preoperative MRI scan and intraoperative 5-ALA) improves the functional outcome postoperatively	WHO performance status MOCA Barthel Index MRC grading of power in all 4 limbs	5 days post-op., or discharge date (whichever is soonest); 6wks post-op.,3mths post op. and then 3mthly up to 24 months
Secondary	Assess the correlation of proxy to participant classification assessment of quality of life	At a minimum, answers to questions 29 and 30 of the QLQ-C30 Ideally answers will be provided to all of the QLQ-C30 and BN20.	Baseline, 5 days post op or discharge date (whichever is soonest); 6wks post op, 3mths post op. and then 3mthly up to 24

	Objectives	Outcome Measures	Timepoint(s)
			months. Proxy will not complete questionnaires when participant stops completing them.
Tertiary – Mechanistic Study Objectives – on a sub-set of participants	Sensitivity and specificity of the anatomico-spatial location of DTI fibre tracts compared with intraoperative direct electrical stimulation or Motor evoked potential changes in patients undergoing awake surgery	Sensitivity and specificity calculation using pre and post-surgery MRI images	Analysis will be undertaken post-surgery.
Tertiary – Mechanistic Study Objectives – on a sub-set of participants	Sensitivity and specificity of NiUS to identify the tumour boundary when compared with 5-ALA and post-operative MRI scan. Navigated biopsies will be taken from tumour boundary tissue planned for resection.	Intra operative NiUS images and post-operative MRI scans and Intraoperative biopsy samples	Analysis will be undertaken post-surgery when biopsy results are available.

7. STUDY DESIGN

7.1. Stage 1: non-randomised multicentre learning and evaluation stage (IDEAL Stage IIB study)

This is a non-randomised multicentre learning and harmonisation stage in which quality control measures and mentoring will be employed to improve and evaluate standards of practice (IDEAL Stage IIB Study).[50,51] The IDEAL Stage IIB study will determine whether surgeons using the technologies employed in the randomised controlled trial demonstrate acceptable expertise in delivering the new approach prior to proceeding with the randomisation stage.

Stage 1 is divided into 3 components:

1. Pre-trial Webinar (see section 9.1.1)
2. IDEAL Stage IIB (Quality assurance, Mentoring and Trial centres evaluation) (see section 9.1.2)
3. End of Stage 1, Pre-Stage 2 RCT, 1-day Symposium (see section 9.1.3)

The IDEAL Stage IIB study will comprise the following:

- Mentoring for local site surgeons.
- Quality assurance of operative procedure.

Mentoring by the CI and Co-CIs will be provided through visits to participating centres and frequent participant meetings, together with a helpline for individual advice sessions from the CI and Co-Cis and co-applicants, as appropriate. Neurosurgeons will contribute data to ensure standardisation of the protocol and acceptable expertise in delivering the new approach. This will be evaluated using the following metrics: operation length; successful use of DTI neuronavigation and frequency and duration of NiUS use to achieve complete tumour resection without major neurological deficit; and extent of tumour resection assessed on postoperative MRI scan. The number of cases required for this may vary, but is expected to be small as most surgeons are already familiar with the component techniques and are not anticipated to require substantial assessment. Ensuring all participating surgeons are ready to take part will minimize performance bias in Stage 2 and ensure standardisation of intraoperative technique.

7.2. Stage 2: prospective, Stage III, multicentre randomised controlled trial with internal pilot

This is a parallel group two arm, multicentre, randomised controlled trial. See Appendix A for a Flowchart depicting the flow through the trial.

Population: 357 participants with GB suitable for maximally resective surgery (attempted gross total resection of all enhancing tumour), as agreed at the local Neuro-oncology Multi-Disciplinary Team meeting.

Intervention: standard care surgery (neuronavigation based on preoperative imaging and intraoperative use of 5-ALA) with the addition of DTI neuronavigation and NiUS.

Control: standard care surgery (neuronavigation based on preoperative imaging and intraoperative use of 5-ALA)

Outcome: Deterioration Free Survival

Setting: UK NHS Trusts undertaking GB surgery

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Patients aged 18-75 year with a primary GB tumour which is deemed maximally resectable (attempted gross total resection of all enhancing tumour) by the local Neuro-oncology Multi-Disciplinary Team (MDT) meeting, will be potentially suitable for inclusion in the trial.

8.2. Inclusion Criteria

- Age 18-75 years
- 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)

- Patient is suitable for concomitant 6 weeks adjuvant radiotherapy and Temozolamide (TMZ) chemotherapy or adjuvant TMZ at the time of MDT decision
- Willing and able to give informed consent
- Able to understand written English to enable completion of trial questionnaires (Stage 2 only)
  Note: This is a requirement as one of the outcome questionnaires in not available in all of the UK national languages; specifically BN-20 is currently not available in Welsh
- Able to provide a proxy who is willing to complete questionnaires as requested (Stage 2 only).

8.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Midline/basal ganglia/cerebellum/brainstem GB
- Multifocal GB
- Recurrent GB
- Suspected secondary GB
- Contraindication to MRI

9. PROXY INCLUSION (Stage 2 only)

It is widely recognised in quality of life research that an individual may measure their quality of life differently from how another person would do, even if that person is close to the individual (e.g. carer, partner etc.). We have therefore set the study up so that we can collect both the participants own assessments (as they are able to provide them), and also the proxy/participant's assessment. By doing so we will be able to explore potential difference in assessment between the two particularly with regards to deterioration of quality of life. This require both assessments to be collected whenever possible.

The proxy/participant assessment is also important as it will be collected for the small subset of individuals who are not able to complete the quality of life questionnaires but do not lose capacity, have disease progression or die until sometime later. Thus, providing a measure of the quality of life which in the absence of the patients is the next best measure.

It is vitally important in terms of the study's validity to be able to collect data on quality of life, death and time to progression to the point of death to the end of the follow-up, hence the need to include a Proxy in this study and has start and end questionnaire data.

Proxies will receive questionnaires as per the schedule in 10.7.4. The quality of life questionnaires will be the same as those given to the participant except in the third rather than first person.

(Note where a participant dies, loses capacity or withdraws from the study – this will also automatically cease the proxy's involvement in the study).

9.1. Inclusion Criteria

- Age 18-75 years
- Nominated by an individual who has consented to participate in Stage 2
- Willing and able to give informed consent
- Able to understand written English to enable completion of trial questionnaires

10. PROTOCOL PROCEDURES

10.1. Stage 1: non-randomised multicentre learning and evaluation Stage (IDEAL Stage IIB study)

Patients will be recruited at each centre following the same procedures as detailed in Sections 10.2 to 10.6 (see below for variation in consent information). They will undergo the same pre-operative assessment as patients in Stage 2. All Stage 1 patients will undergo standard care surgery and in addition NiUS and DTI, which will be used in the experimental arm of the Stage 2 trial. Awake surgery will be used at the discretion of the operating surgeon. Postoperative assessment by MRI scan and assessment of any complications will be performed the same as in Stage 2, including evaluation of DTI and iUS images versus post-operative MRI assessment.

Stage 1 is divided into the following three components:

10.1.1. Pre-Stage 1 Stage Webinar or Symposium

At the start of Stage 1, a Webinar or Symposium will be held at which expert providers and practitioners will demonstrate and discuss the use of DTI and NiUS expected in the study. In the case of DTI, neurosurgeons will be updated on the latest MRI/DTI sequences, intraoperative DTI neuronavigation software (BrainLAB Elements or Medtronic Stealth), and the clinical application with case examples and white fibre tract surgical anatomy refreshed. Variations in clinical MRI hardware mean it will not be possible to fully eliminate variance in diffusion data collected across all study sites. However, every effort will be made to standardise the sequence acquisition parameters; each site will be asked to acquire a routine diffusion acquisition with 32 evenly-distributed diffusion directions at a b-value of 1000 s/mm^2 and a resolution of 2x2x2mm.

Guidance will be provided on minimum necessary diffusion processing and analysis using the BrainLAB Elements and Medtronic Stealth software in use at each site to maximise standardisation in tractography and image fusion to the neuronavigation system. With respect to NiUS, all recruiting centres already deploy iUS as appropriate, with the use of a range of ultrasound machines. The centres also all have access to probes within the range of 5-10MHz. As probe selection is dependent on the location of the lesion and the overlying craniotomy, it is not possible to stipulate use of the same equipment uniformly. However, this is actually a strength of the study, as should the use of iUS be shown to be beneficial, it allows far more generalisability of the results, and hence global appeal.

The symposium or webinar will permit surgeons to refresh their ultrasonography skills, case study examples from the lead centres, and the opportunity to consult with the ultrasound expert and the Co-CIs using NiUS routinely for tumour resection.

10.1.2. IDEAL IIB Study (Quality assurance, mentoring and trial centres learning).

Mentoring will take place at participating centres through visits as necessary from the expert trial faculty, and arrangements made for e-mail and telephone support where participating surgical teams are less familiar with aspects of the protocol.

Participants will be recruited at each centre following the same procedures as detailed in Sections 10.2 to 10.6. The number of cases required for this may vary, but is expected to be small for most surgeons, as the participating centres are already familiar with the component techniques.

10.1.3. 1-Day Pre-RCT Webinar or Symposium.

One month prior to the planned completion of Stage 1, Co-applicants, all participating centre Principal Investigators, and Industry supporting partners (Brainlab Pvt Ltd and Medtronic Plc) will meet via a Webinar or symposium hosted by the Lead Investigators and the Surgical Interventional Trials Unit (SITU). This will review progress and initial data from Stage 1, with particular focus on the experimental interventions, namely DTI neuronavigation and NiUS. Surgeons will have the opportunity to discuss the quality standards for the interventions. The discussion of early results and experiences will permit group learning, which may be used to update/refine the protocol for the Stage 2 part of the trial. In addition, any concerns raised by experience during Stage 1 about (a) participant inclusion criteria (b) acceptable variations in intra-operative practice will be discussed in the light of the early results, and modifications made to this protocol if necessary.

10.2. Recruitment

10.2.1. Participants

Recruitment into the trial will be undertaken in two phases in conjunction with the separate stages of the trial. There will be a separate Patient Information Sheet and Consent Form for patients entering Stage 1 (IDEAL IIb) and Stage 2 (RCT).
Note: The stages are sequential at participating sites and the stages cannot be recruited to in parallel.

Posters advertising the trial will be displayed in electronic and paper formats as allowed in participating sites. All potentially eligible participants will have the trial mentioned at the same time the options regarding their surgery are discussed in dedicated neuro-oncology clinics. Depending upon the site, the resources available, and most importantly how the participant is dealing with their diagnosis, the recruitment process and approach may vary across and within sites. Potential participants may straight away be provided with the trial participant information sheet and asked to consider the trial, and that a member of the local research team will contact them. It may be the case that individuals are asked if it would be acceptable for their name to be passed to the research team who will make contact at a later timepoint, or potential participants may be given the participant information sheet and asked to call the number on it if they wish to find out more about the trial.
Note: When a potential participant is approached for verbal consent for their details to be passed onto the local research team – if this consent is given this should be recorded in their clinical notes.

The local and co-ordinating team's details will be on the participant information sheet so that individuals and their families can make contact to have any questions/queries answered. In addition, brain tumour charities will be contacted to promote and display information regarding FUTURE-GB. Furthermore, both OCTRU and SITU have twitter feeds which will be utilised to promote the trial, and acknowledge when milestones are met (i.e. sites open to recruitment, first recruitment at a site, 10% of recruitment, 100 patients recruited etc.) Also, it is anticipated that patient bodies who have their own social media feeds may post about the trial.

10.2.2. Sites

Sites that would like to participate in the trial will be required to complete a site feasibility questionnaire, deliver GB surgery, and have access to the technology being utilised in the trial. Site feasibility will be assessed on an individual unit basis, however research experienced and research naïve sites will be

included. Those sites assessed as being suitable will recruit participants initially into Stage 1 and then proceed to recruit participants to Stage 2.

10.3. Screening and Eligibility Assessment

Following screening and consent, participants will be entered into the Stage that is currently open at their site.
Note: Screening should only be undertaken by those listed on the trial screening log, where individual site Principal Investigators' have delegated this trial responsibility. Eligibility checks will involve checking that participants meet all inclusion criteria and none of the exclusion criteria.

There will be no waivers regarding eligibility, i.e. each participant must satisfy all the approved inclusion criteria of the protocol. Changes to the approved inclusion and exclusion may only be made by a substantial amendment to the protocol.

10.4. Informed Consent - Participant

The participant must personally sign and date the latest approved version of the Consent form before any trial specific procedures will be performed. Due to different timelines used at sites, the exact timing and location of the consent may vary – however as a minimum, consent must be given before a participant undergoes the routine pre-operative imaging as the participants needs to have been randomised by this Stage to ensure that all imaging required is undertaken. Patient Information Sheets will differ slightly between Stage 1 and Stage 2: In Stage 1 the purpose of the Stage within the overall Trial will be explained and it will be made clear that randomised allocation of treatment will not occur – all entrants will receive the experimental treatment protocol, but reduced follow-up.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The potential participants will be allowed as much time as desired to consider the information and will also be given the opportunity to question the Investigator/ a member of the research team, their GP or other independent parties to decide whether they will participate in the trial. However, neither the trial, nor time to think about participating in the trial, should cause a delay to any surgery to be undertaken. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Consent. The person who obtains the consent must be suitably qualified and experienced and have been authorised to take consent by the site's Principal Investigator. A copy of the signed Consent Form will be given to the participant, a copy placed in the medical notes, and the original will be retained at the study site.

At the same time as taking consent in Stage 2 only, the participant will be asked to provide the name of a proxy, such as a friend/relative/spouse who they would nominate to also answer questions about a patient's quality of life. This individual will be given a separate Information Leaflet and asked to sign a

separate proxy consent form. To enter Stage 2, the participant must have a proxy who agrees to consent to also participate in FUTURE-GB, by questionnaire completion.
Note: If at some point a patient wishes to change their proxy, or the proxy needs to change, for example their contact reduces with the patient, the proxy can suggest another proxy to be approached for consent and questionnaire completion.

10.4.1. Informed Consent – Proxy (Stage 2 only)

The proxy must personally sign and date the latest approved version of the Consent form. Due to different timelines used at sites, the exact timing and location of the consent may vary – however as a minimum, consent must have been given before the individual they are the proxy to undergoes the routine pre-operative imaging.

Written and verbal versions of the Proxy Participant Information and Informed Consent will be presented to the potential proxy participants detailing: the exact nature of the trial; what it will involve for themselves; and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. It is anticipated that these will initially be given to the participant to decide who they will ask to be their potential proxy. It is also anticipated that the potential proxy may well be the person attending the standard clinic appointments with the participant.
Note: There is no specific requirements on who can act as a proxy for a participant – this includes relationship to the participant, time known to the participant, time spent with the participant each week

10.4.2. COVID consenting – all stages

Due to pandemic-related changes in clinic operations and people permitted to accompany patients, the option of eConsenting is being given in both stages of the trial, for the duration of the need for COVID-safe practices at participating Trusts. This means that interested participants and proxies would have the option of completing the consent online, via a secure link, as well as the option of completing it in clinic as previously detailed. Participants (and proxies if COVID-measures still in place) would be asked for their email address after initial approach from the clinical research team, and an email sent through which they could complete the eConsent as a secure online form, and also to have a copy emailed to themselves as a pdf. This would allow more time for participants to consider the trial and talk to their proxy if needed. Robust procedures would be in place to ensure that participants would not be able to be registered/randomise if this consent was not already in place.

10.5. Randomisation

Randomisation of patients will only occur in Stage 2 of the trial. Every centre and each participating surgeon will offer surgery under both arms of the trial.

Randomisation will be via the web-based service provided by the Oxford Clinical Trials Research Unit (OCTRU), using the method of minimisation. The minimization factors will be trial site, age (≤ 55 yrs or > 55 yrs), expected surgery status (under general anaesthesia or awake), and eloquence of tumour location (non-eloquent or eloquent).

Participants will be randomised after having given written consent, however they will remain blinded as to which arm of the trial they have been allocated. The local clinical team at site will receive an email from the randomisation system detailing the arm of the trial to which a participant has been randomised. Randomisation has to occur before the pre-operative imaging takes place so that the assigned trial pre-operative imaging can be undertaken.

Participants will be randomised 1:1 to either:

- Standard care surgery (neuronavigation based on preoperative imaging and intraoperative use of 5-ALA) (Control arm)
- Standard care surgery (neuronavigation based on preoperative imaging and intraoperative use of 5-ALA) **AND** of DTI neuronavigation and NiUS (Intervention arm)

The participant's identifiable information will be recorded on the randomisation form, and will be uploaded to an encrypted, separate database at the University of Oxford.

10.6. Blinding and code-breaking

Stage 1 is not blinded; the participants will be receiving all of the technologies during their surgery.

In Stage 2, the participant will be blinded to the allocation (intervention or control arm), and the treating clinician will be aware, as he/she needs to perform the surgery with the intraoperative technologies as allocated. In addition to the participant, the radiologist (reviewing the postoperative MRI) will be blinded to the trial arm. Given this, only on the operation CRF will data of the allocation be included.

There is no code breaking procedure required, as the intervention is a single time point application for the duration of the participants' surgery. If there are any complications/issues that arise post-operatively, the arm to which the patient has been allocated will not affect any subsequent actions undertaken by the participant's clinical care team.

10.7. Description of study intervention(s), comparators and study procedures (clinical)

The intervention comprises standard care surgery (neuronavigation based on preoperative imaging and intraoperative use of 5-ALA) with DTI neuronavigation and NiUS. The comparator is the control, which is standard care surgery (neuronavigation based on preoperative imaging and intraoperative use of 5-ALA). Surgery will be undertaken, using the technology allocated.

10.7.1. Description of study intervention(s)

The planned experimental intervention is: GB tumour resection using standard care surgery (i.e. neuronavigation based on preoperative imaging and intraoperative use of 5-ALA), with the addition of DTI neuronavigation and NiUS. All patients entering Stage 1 will receive this intervention.
Note: An imaging manual will be available to sites.

10.7.2. Description of comparator(s)

The control intervention is: GB tumour resection using standard care surgery (i.e. neuronavigation based on preoperative imaging and intraoperative use of 5-ALA).

10.7.3. Description of study procedure(s) – Stage 1

All patients will undergo a routine preoperative neuronavigation scan. All patients will have a DTI scan (additional 5 minutes).

There will be minimal deviation from the standard care pathway for GB patients undergoing resective surgery. Awake surgery and/or that using intraoperative electrophysiological monitoring is permitted as clinically indicated. Surgery will be performed by a dedicated neuro-oncology surgeon. There is no alteration to the standard radiotherapy and chemotherapy dosing regimen or treatment schedule for participants. Postoperative assessments will be undertaken pre-discharge (5 days post-operatively, or at discharge).

Within 72 hours of surgery, patients will undergo an MRI with contrast, permitting a volumetric evaluation of residual contrast enhancing tumour, which will be recorded. Further follow up MRI scans will be undertaken at 6 months postoperatively, and 3 monthly thereafter as per standard care pathway.

Time point from Operation	Data	Data Collection Method
At discharge.	Surgical complications and serious adverse events	NIHR research nurse / local clinical team at routine appointment on trial CRFs
6months	Surgical complications and serious adverse events	NIHR research nurse / local clinical team at routine appointment on trial CRFs

10.7.4. Description of study procedure(s) – Stage 2

All participants will undergo a routine preoperative neuronavigation scan. Those participants randomised to the experimental arm, will have a DTI scan (additional 5 minutes).

All participants will have preoperative assessments that will comprise: HRQoL (EORTC QLQ-C30[15,16] and BN20[17]) and functional performance status (WHO performance status,[55] MOCA,[56] Barthel Index,[57] MRC power grading of limbs). Additionally, baseline data will be collected including sex, weight, height, MGMT methylation status, hand dominance, date of primary diagnosis and tumour location.

Proxies will be asked to provide their relationship to the participant, the time on average they spend with the participant and any comments they wish to make about the participant's cancer journey.

Within 72 hours of surgery, patients will undergo an MRI with contrast, permitting a volumetric evaluation of residual contrast enhancing tumour, which will be recorded. Further follow up MRI scans will be undertaken at 6 months postoperatively, and 3 monthly thereafter as per standard care pathway. The patient, radiologist (reviewing the postoperative MRIs), will be blinded to study arm.

Surgery will be undertaken, using the technology allocated. Awake surgery and/or that using intraoperative electrophysiological monitoring is permitted in either group, as clinically indicated. Surgery will be performed by a dedicated neuro-oncology surgeon, who has participated in Stage 1 of the trial. There will be minimal deviation from the standard care pathway for GB patients undergoing resective surgery, and no alteration to the standard radiotherapy and chemotherapy dosing regimen or treatment schedule for participants. Data will be collected on the operation performed and histology reported locally at site. Postoperative assessments will be undertaken pre-discharge (5 days post-

operatively, or at discharge), and at six weeks post randomisation, with 3 monthly assessments subsequently. Survival will be tracked for 24 months.

Once the patient has been randomised, the chance of intra operative crossover is very small, and would only arise if there was an unexpected surgical complication, whereby the surgeon during the operation considered he/she required the use of ultrasound. If this occurred, this would be a protocol deviation, and should be reported to the trial team.
Note: DTI cannot be performed during surgery, and therefore this does not apply.

The Strummer et al. surgical trial,[24] which evaluated a similar change in surgery-related practice, did not report any crossover due to surgeon equipoise, and only in 2 of 322 patients was there a technology issue.

The schedule of trial assessments and methods for data collection are described in the table below after consent has been given. As per standard practice, those undertaking any trial assessments/data collection – should establish that the participant still has capacity to continue to decide to participate in the trial:

Time point from Randomisation	**Data**	**Data Collection Method**
Baseline	HRQoL (EORTC QLQ-C30 and BN20)	Participant and proxy will complete questionnaires
	Functional performance status (WHO performance status, MOCA, Barthel Index, MRC power grading of limbs)	NIHR research nurse / local clinical team
5 days post-op., or at discharge, 6 weeks, 3,6,9,12,15,18,21 and 24 months	HRQoL (EORTC QLQ-C30 and BN20) *	Participant* and proxy will self-complete questionnaires in the hospital
	Functional performance status (WHO performance status, MOCA, Barthel Index, MRC power grading of limbs)	NIHR research nurse / local clinical team on trial CRFs
	Surgical complications and serious adverse events	NIHR research nurse / local clinical team on trial CRFs
24 months	Mortality data§	NIHR research nurse / local clinical team on trial CRFs

** NOTE: Due to the natural progression of this disease, a participant may not be able to complete the questionnaires at all or in their entirety. It is hoped that the full questionnaire pack is completed, however for the primary outcome, only 2 of the questions in the questionnaires are required to be answered as the primary outcome is based on just one of the DFS domains that is part of the questionnaire. Proxies will be contacted for completion of the questionnaires for each time point applicable to the participants for whom they are a proxy*

§ Progression of disease and occurrence of death are the universal outcome measures by which cancer treatments are assessed to enable the study to report overall survival rates for the study. These have to be collected to fulfill the widely held standards for cancer-based research in this area.

The specific questions that need to be answered for the primary outcome are:

Please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7 Very poor to excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7 Very poor to excellent

10.11. Imaging Schedule for both Stage 1 and 2

Time point	Imaging	Part of Standard Care?
Preoperative	Neuronavigation MRI scan (T1 with contrast) Aim: to facilitate surgery	Yes, however, if part of Stage 1 or randomised to experimental arm, this will include a DTI scan (which may add up to 5 minutes to the MRI scan)
Postoperatively (within 48-72 hours of surgery)	Diagnostic MRI (T1 +/- contrast) Aim: to determine extent of resection as a % of preoperative contrast enhancing tumour volume	Yes
6 months	Diagnostic MRI (T1 +/- contrast) Aim: to assess response following concomitant radiotherapy and chemotherapy	Yes
Subsequent 3 monthly follow up scans	Diagnostic MRI (T1 +/- contrast) Aim: to assess response following adjuvant chemotherapy and detect early tumour recurrence	Yes

10.12. Sample Handling

All participants in both Stage 1 and Stage 2 of the trial will have biopsy samples taken from their tumour as standard of care (tumour surface, tumour core and margin). This includes, as appropriate, samples from tumour margin tissue planned for resection, where no fluorescence is seen, but the NiUS image shows signal change suggestive of possible tumour/abnormal tissue (those patients in Stage 1 and in the experimental arm of Stage 2). These biopsies will be sent to the pathology lab as per standard protocols/guidelines at each participating centre. No special precautions are required when handling these tissue samples.

10.13. Early Discontinuation/Withdrawal of Participants

10.13.1. Stage 1

Principal investigators may withdraw participants for the following reasons:

1. If, following consent but prior to surgery, a participant decides to refuse surgery.
2. If, following consent but prior to surgery, a clinician decides that resective surgery is no longer considered in the participant's best interests.

If participants are withdrawn from their interventions for these reasons, they will continue to be followed up in line with the protocol.

Participants may also withdraw from the trial intervention and some or all of the follow-up at any time, without this affecting their clinical care. Where appropriate, remote follow-up and reasons for withdrawal will be collected where possible. As there is no set sample size for this part of the study, participants that withdraw will not be replaced.

All data and samples collected for the purposes of the study will be retained by the trial team.

10.13.2. Stage 2

Principal investigators may withdraw participants from their randomised intervention for the following reasons:

1. If, following consent but prior to surgery, a participant decides to refuse surgery.

2. If, following consent but prior to surgery, a clinician decides that resective surgery is no longer considered in the participant's best interests.

3. During surgery if, for an unforeseen reason, the surgeon decides it is in the best interest of the participant that the use of NiUS or iUS will facilitate surgery above that which is otherwise possible.

If participants are withdrawn from their interventions for these reasons, they will continue to be followed up in line with the protocol.

Participants may also withdraw from their randomisation intervention and or some or all of the follow-up at any time, without this affecting their clinical care. Where appropriate, remote follow-up, and proxy-completed data collection will be encouraged. Reasons for withdrawal will be collected where possible. The type of withdrawal and reason will be recorded in the CRF. All data and samples collected for the purposes of the study will be retained by the trial team.

Participants who withdraw will not be replaced, as a loss to follow-up allowance has been included to allow for sufficient numbers to be analysed. Replacements will however be recruited if requested after a DSMC review.

If a participant withdraws from the study or loses capacity, this will cease also all contact with their proxy and no further contact will be made.

10.14. Definition of End of Study

The end of study is the point at which all the study data have been entered, any queries resolved, and a hard data lock has taken place of stage 2.

10. SAFETY REPORTING

The trial will be run in accordance with OCTRU's Standard Operating Procedures (SOPs) and operational policies, which all adhere to applicable UK regulatory requirements. An independent Data and Safety Monitoring Committee (DSMC) and Trial Steering Committee (TSC) will be appointed. The DSMC will monitor data arising from the trial, review confidential interim reports of accumulating data, and recommend whether there are any ethical or safety reasons why the trial should not continue. The TSC will monitor the trial's progress and will provide independent advice. Both committees will comprise independent clinicians, statisticians, health service researchers and patient representatives. The project will also be monitored by the Sponsor (University of Oxford), and progress reports will be submitted to the Funder. Given the nature of the primary outcome and the interest in key secondary outcomes (namely, OS and PFS), no formal interim analyses are planned.

10.1. Definitions

10.1.1. Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical trial participant.
Note: An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporarily associated with the trial procedures, whether or not considered related to the procedures.

10.1.2. Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
Note: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2. Reporting Procedures

It is important to consider the natural history of a high-grade brain tumour affecting each participant enrolled, the expected sequelae of the illness, and the relevance of these complications to the trial treatment. All eligible participants have a poor prognosis, and due to the complexity of their condition

are at increased risk of experiencing multiple adverse events. Consequently, only Serious Adverse Events (SAE) will be recorded in this trial. This is limited to serious adverse events, which might reasonably occur as a consequence of the trial treatment (i.e. not events that are part of the natural history of the primary disease process or expected complications of a brain tumour).

SAEs, as defined above, experienced by a participant from their enrolment until their completion of the trial must be reported in the participant's medical notes, on the trial CRF, and reported to the CTU using the SAE Reporting Form, within 24 hours of observing or learning of the SAE(s). All sections of the SAE Reporting Form must be completed.

A SAE occurring to a participant will be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form

10.2.1. Events exempt from being reported as SAEs

The following hospitalisations are not considered a SAE:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- admissions as per protocol for a planned medical/surgical procedure
- admissions for planned chemotherapy and/or radiotherapy and any related sequelae
- routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
- disease progression where not considered to be related to study intervention

10.3. Death during the study

Death due to disease under study is to be recorded on the Death CRF form providing the death is not unexpected or if a causal relationship suspected. The investigator must clearly state whether the death was expected or unexpected and whether a causal relationship to the study intervention or other protocol treatment intervention is suspected.

10.4. Elective admissions and supportive care

Elective admissions to hospital for patient convenience or for planned procedures or investigations or treatment as specified in this protocol and standard supportive care are not SAEs, and do not require SAE reporting.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here, with details fully described in a statistical analysis plan (SAP). The SAP will be agreed to by the TSC, with input from the DSMC, prior to unblinding of trial results to the team. The SAP will be finalised prior to the final analysis taking place, and prior to unblinding of trial results to the team.

11.2. Description of the Statistical Methods

The analysis of the primary outcome will be a time-to-event analysis using a mixed effect Cox proportional hazard regression model. Minimisation factors (age, site, anticipated patient operative state and tumour location), radiotherapy, and MethylGuanine-DNA MethylTransferase (MGMT) status will be adjusted for as fixed effects. Centre will be included as a random effect.

The assumption of proportional hazard for the Cox model will be examined. If the proportional hazard assumption is not met, parametric survival analysis, such as the accelerated failure time method will be considered. A sensitivity analysis will look at the impact of adjusting for surgeon instead of centre. Secondary analysis will explore the influence of progression as an event by assessing DFS minus progression. An unadjusted comparison using a log-rank test will also be carried out. Kaplan-Meier curves will also be generated. Secondary Time-to-event outcomes (e.g. Overall Survival) will be analysed in a similar manner.

Quality of life amongst survivors will be quantified without a formal statistical comparison between treatment groups.

There are multiple factors that may influence how a patient rates his/her HRQoL, which may be related to factors other than the intervention. However, by using a randomized trial design, it is assumed that patients in both treatment arms are comparable on all aspects, both measured (e.g. age, performance status) and unmeasured (e.g. mood, coping strategy, personality). This means that the impact of the psychological state on the evaluation of HRQoL is treated as similar for the two trial arms. Thus, the study will be able to measure whether the experimental intervention has an impact on HRQoL when compared to patients receiving standard treatment.

11.3. Sample Size Determination for IDEAL IIB Study (Stage 1)

There is no formal sample size for the IDEAL study. Participants will be recruited at each centre, the number of cases required from each centre will vary depending upon caseload numbers and the number of neurosurgeons, but is expected to be small for most sites (<5), as the participating centres are already familiar with the component techniques.

11.4. Sample Size Determination for the RCT (Stage 2)

The sample size is based on the primary outcome of DFS based upon the global health status domain in the QLQ-C30 questionnaire, version 3,[18,53,54] as previously defined, and achieving a statistical power of 90% for the primary analysis (see below) with 2-sided significance level of 5%.

Assuming a Hazard Ratio (HR) of 0.7, median DFS survival time of 5 months in the control arm, 24 months follow-up on all participants and allowing for 5% loss to follow-up occurring by month 3, this yields an overall target of 357 participants (178/179 per arm; 335 events overall) (Stata "artsurv" www.stata.com). The global health status DFS outcome had median survival times of 6 months in the standard treatment arm (surgical resection with standard radiotherapy and chemotherapy) group in a recent trial.[18] Additionally, the observed HR was 0.64, 95% CI (0.56, 0.74) for the DFS measures in this trial suggesting that a HR of 0.7 as assumed above is a plausible magnitude of effect to be observed for this population.[58] It would also be one which would be considered important to clinicians and patients given the definition of a DFS event (death, progression or a patient anchor determined clinically meaningful deterioration of 10 points).

For key secondary outcomes (i.e. the other four DFS outcomes, PFS and OS) there is over 80% power for this size of study, assuming a median overall survival time of 6-9, 7 and 15 months respectively in the control arm,[5] a HR of 0.70 for both, and other inputs as per above.

11.5. Recruitment Predictions for the RCT (Stage 2)

15 NHS Trusts have already agreed participation in the study. These centres collectively review approximately 1600-1866 GB patients per year (2531 cases diagnosed in 2015 with projected 6% annual rise).[59] Assuming 40% of patients are deemed suitable for maximal resective surgery, and allowing trial exclusion criteria, this creates a potential annual pool of 600-700 patients. Brain tumour research recruitment rates are often over 50%, higher than the typical 33%. Therefore, conservatively, it is anticipated that 250-300 patients/year could enrol. 15 centres have up to 25 dedicated neuro-oncology surgeons and it is predicted that each site may recruit on average 1 participant per month. A total of 357 patients will be recruited across a minimum of 15 sites. The trial documentation and procedures will be developed together with patient representative input, and OCTRU involvement, to ensure optimum recruitment rates.

	Months of recruitment																										
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Hospital 1	0	1	0	1	1	1	2	2	2	1	2	1	1	2	2	2	2	2	1	1	2	2	1	2	2	1	2
Hospital 2	0	1	1	1	0	1	1	2	2	1	2	2	1	1	2	2	2	2	1	2	2	1	2	2	2	2	2
Hospital 3			1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hospital 4			0	1	0	1	0	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hospital 5			1	0	1	1	1	1	1	1	0	1	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1
Hospital 6					1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hospital 7					1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hospital 8					1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hospital 9					1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hospital 10					1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hospital 11						0	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hospital 12						0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hospital 13						0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hospital 14						1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Hospital 15						1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Monthly recruitment	0	2	3	3	8	11	13	16	13	13	15	16	14	16	17	17	17	16	15	16	17	16	16	17	17	16	17
Cumulative recruitment	0	2	5	8	16	27	40	56	69	82	97	113	127	143	160	177	194	210	225	241	258	274	290	307	324	340	357

11.6. Analysis populations

The principal analysis will be performed once data collection is completed and on the intention to treat (ITT) population, whereby participants will be analysed according to their randomisation allocation, irrespective of compliance with the protocol. If appropriate, additional analysis population, such as a per protocol population (PP), will be defined in the statistical analysis plan. A PP population may exclude participants who deviate from specific aspects of the protocol.

11.7. Decision points

11.7.1. Stage 1 (IDEAL IIB study)

Up to 5 participants need to have been recruited from a site and evaluated by the IDEAL team for the site to be allowed to proceed to open to recruitment of Stage 2.

11.7.2. Stage 2 (RCT)

Built into the trial is an internal pilot of recruitment to the RCT (Stage 2). There will be a formal stop/go review after 12 months of recruitment to the RCT to review the number of randomisations over the pilot period. If the target of at least 80 randomisations has been met, the trial will continue to recruit for a further 15 months. Data from the 80 patients will be included in the final analysis. All Stage 2 patients will be followed up to 24 months after randomisation.

The following stop-go criteria are proposed for the Trial Steering Committee (TSC) after 12 months of recruitment:

	actual recruitment after 12 months of recruitment		
target = 80	**>80 participants**	**65 - 80 participants**	**<65 participants**
recruitment rate (per centre per month)	0.6	0.45	0.37
stop-go criteria	recruitment feasible proceed with study	review recruitment strategies report to TSC continue but modify and monitor closely	recruitment not feasible decision not to proceed

The TSC and the funder would make the final decision to terminate the trial.

11.8. Stopping rules

11.8.1. Stage 1 (IDEAL study)

There are no formal stopping rules for this Stage of the study.

11.8.2. Stage 2 (RCT)

Given the nature of the primary, and key secondary, outcomes and the planned study length, no formal interim analyses with stopping guidelines are planned. An independent Data Safety and Monitoring Committee (DSMC) will review the accumulating data at regular intervals and may recommend pausing or stopping the trial in the event of safety concerns.

11.9. The Level of Statistical Significance

All principal analyses will be performed at the 2-sided 5% significance level.

11.10. Procedure for Accounting for Missing, Unused, and Spurious Data.

The procedure for handling spurious or missing data will be described in the Statistical Analysis Plan, and the Data Monitoring Plan. The trial will attempt to collect data as completely as possible.

The main analysis will include participants for whom endpoint data are available, with other participants being censored after their last available relevant outcome measure. Sensitivity analyses will examine the effects of alternative assumptions about the missing data.

11.11. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation(s) from the original statistical plan will be described and justified in the final report, should these occur.

11.12. Health Economics Analysis

There are no health economic analyses to be undertaken as part of the trial.

12. DATA MANAGEMENT

A data management and sharing plan will be produced for the trial in accordance with OCTRU Standard Operating Procedures (SOPs), this will include reference to confidentiality, access and security arrangements.

All data will be processed following the SOPs, which have been written in line with all applicable regulatory requirements. All trial-specific documents, except for the signed consent form and follow-up contact details, will refer to the participant with a unique study participant number/code and not by name. Participant identifiable data will be stored separately from study data, and in accordance with OCTRU SOPs. All trial data will be stored securely in offices only accessible by swipe card by the central coordinating team staff in Oxford, and authorised personnel.

Data will be collected from participants and proxies via questionnaires and case report forms that will be returned to the central trial office in Oxford, via post using a pre-addressed freepost envelope, or NHS email as appropriate, or directly into an online secure database – the study's dedicated instance of REDCap. In addition, participant images will be stored within the cloud database Quentry (BrainLab AG). As a third-party processor BrainLab will not receive any data that could identify participants.

Participant data will be stored and transported in accordance to SOPs. Upon completion of the trial, fully de-identified research data may be shared with other organisations at the behest of the funder.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, scans, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent and follow-up contact details, the participant and proxy will be referred to by the study participant/proxy number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Where data is submitted directly to the trial office, contemporaneous access by local research teams to the online database will enable the local research teams at sites to download copies of their participants' data.

12.3. Data Recording and Record Keeping

The data will be stored and used in compliance with the relevant, current data protection laws (Data Protection Act 2018; General Data Protection Regulation (GDPR) 2018). The trial data (including data for SAEs) will be entered onto a validated REDCap study database developed and maintained by OCTRU and

which can only be accessed by authorised users via the application. The application resides on a webserver hosted and managed by Oxford University's IT Services division. The server is on the university's backbone network and is backed up nightly to a secure off-site location.

After closure of the trial and data analyses, the data will be made publicly available at the time of publication. The Trial Master File will be archived for five years from the end of the study.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and CTU standard operating procedures. This research will be coordinated by the Surgical Interventional Trials Unit (SITU), which falls under the Oxford Clinical Trials Research Unit (OCTRU) and SITU personnel work according to OCTRU SOPs. The OCTRU SOPs and related quality assurance and control procedures will be used by SITU to ensure that the study procedures are assessed and carried out as defined in this protocol.

13.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Study monitoring

Monitoring will be performed following a central monitoring and audit plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents.

13.3. Study Committees

13.3.1. Data & Safety Monitoring Committee (DSMC)

The DSMC will meet regularly throughout the trial at time-points agreed by the Chair of the Committee and the CI. At a minimum this will be on an annual basis. The DSMC will review the safety data generated, including all adverse events, and make recommendations as to whether the protocol should be amended to protect patient safety. Recommendations of the DSMC will be discussed between the CI, TSC, and the Sponsor.

13.3.2. Trial Steering Committee (TSC)

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. The TSC will monitor trial progress and conduct, and will advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data and Safety Monitoring Committee (DSMC) and ultimately carries the responsibility for deciding whether the trial needs to be stopped on grounds of safety or efficacy.

13.3.3. Core Trial Management Group (TMG) for all Stages

The Trial Management Group (TMG) consists of those individuals responsible for the operational management of the trial such as the chief investigators, the clinical trial manager, Chair and Vice Chair of the Surgical Trainee Network and representatives from OCTRU.

The TMG will meet every month throughout the lifetime of the Stage 2 study and will:

- Supervise the conduct and progress of the study, and adherence to the study protocol
- Assess the safety as compiled by SITU and assessed by the DSMC, and efficacy of the interventions during the study
- Evaluate the quality of the study data
- Review relevant information from other sources (e.g. related studies)
- Escalate any issues for concern to SITU, specifically where the issue could compromise patient safety or the integrity of the study or quality of the study data

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from the principles of Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file.

15. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the Chief Investigator, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with the principles of Good Clinical Practice.

16.3. Approvals

Following Sponsor approval, the protocol, consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other Ethical Considerations

In the unlikely event of identifying any additional structural abnormalities on imaging, the scan will be checked by a clinical specialist. If the specialist feels that the abnormality is medically important, they will discuss the implications with the participant, and arrange for further investigations as necessary. Participants will not be informed unless the doctor considers the finding has clear implications for their current or future health.

16.5. Reporting

The Chief Investigator will submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.7. Expenses and Benefits

There is no budget to pay for any expenses incurred as a result of the study. However, study visits at the hospital have been scheduled to coincide with routine clinical appointments.

17. FINANCE AND INSURANCE

17.1. Funding

This trial is funded by NIHR Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and Social Care.

The trial is supported by Industry partners BrainLab Pvt Ltd and Medtronic Plc. The Industry partners will provide software/hardware/personnel support during the trial. Contract agreements have been put in place between BrainLab, Medtronic and the University of Oxford as sponsor of the trial.

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the National Institute for Health Research – Efficacy and Mechanism Evaluation Programme. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DISSEMINATION POLICY

The trial has been prospectively registered, prior to ethics approval, on the International Standard Randomised Controlled Trial Number register. The trial protocol will be published in an open-access peer-reviewed journal in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement (SPIRIT, www.spirit-statement.org/). The trial results will be published in an open-access journal, in accordance with the NIHR's policy on open-access research. The study will be reported following the Consolidated Standards of Reporting Trials guideline (CONSORT, www.consort-statement.org), in particular the extensions for non-pharmacological interventions, patient-reported outcomes and pilot and feasibility studies. The Template for Intervention Description and Replication (TIDieR) statement will be used for reporting the intervention,[57] ensuring that replication is possible.

20. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The protection and exploitation of any new IP is managed by the University's technology transfer office, Oxford University Innovations.

21. ARCHIVING

During the clinical trial and after trial closure the Investigator will maintain adequate and accurate records to enable the conduct of the clinical trial and the quality of the research data to be evaluated and verified. All essential documents will be stored in such a way that ensures that they are readily available, upon request for the minimum period required by national legislation or for longer if needed. The medical files of trial subjects will be retained in accordance with applicable national legislation and the host institution policy.

Retention and storage of laboratory records for clinical trial samples will also follow these guidelines.

It is the University of Oxford's policy to store data for a minimum of 3 years from publication. Investigators may not archive or destroy study essential documents or samples without written instruction from the trial office.

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23. APPENDIX A: STUDY FLOW CHART

Stage 1
Non-randomised multicentre learning curve and evaluation phase (IDEAL Phase IIB study)

Stage 2
Prospective, Phase III, multicentre randomised controlled trial with internal pilot
Randomised (n=357)
Adults (18-75 yrs) scheduled to undergo maximal surgery for a primary high-grade brain tumour (Glioblastoma)

Control Group (n=178)	Treatment Group (n=179)
Surgery using standard neuronavigation and 5-ALA	Surgery using Standard neuronavigation and 5-ALA with the addition of Intraop DTI and iUS
Follow up at 72 hours MRI (standard care)	**Follow up at 72 hours** MRI (standard care)
1-7 days post surgery QoL and Physical ability	**1-7 days post surgery** QoL and Physical ability
Follow up at 6 months MRI (standard of care), HR-QoL, Complications and adverse events, Functional performance status.	**Follow up at 6 months** MRI (standard of care), HR-QoL, Complications and adverse events, Functional performance status.
Follow up at 9, 12,15, 18,21,24 months MRI (standard of care), HR-QoL, Complications and adverse events, Functional performance status. Mortality status	**Follow up at 9, 12,15, 18,21,24 months** MRI (standard of care), HR-QoL, Complications and adverse events, Functional performance status. Mortality status

Abbreviations: 5-ALA – Aminolevulinic acid; DTI – Diffusion tensor imaging; iUS – Intraoperative ultrasound; MRI – magnetic resonance imaging; QoL – quality of life.

Two Mechanistic Sub Studies:
1) Sensitivity and specificity of the anatomico-spatial location of DTI fibre tracts compared with intraoperative findings in patients undergoing awake surgery.
2) Sensitivity and specificity of iUS to identify the tumour boundary when compared with 5-ALA, navigated biopsies will be taken from tissue planned for resection.

OUTCOMES: (Tracked for 24 months)
Primary- Deterioration Free Survival ⁎ ‡
Secondary:
- Overall survival ⁎
- Time to Deterioration ⁎ ‡
- Progression free survival †
- Extent of tumour resection on postoperative contrast enhanced MRI †
- Surgical complications and Adverse Events ⁎*
- Number of patients eligible for Adjuvant therapy following surgery (Radiotherapy and Chemotherapy) ⁎*
- Functional outcome post surgery (WHO) performance status, Cognitive ability (MOCA), Physical ability (Barthel Index and MRC power grading in all 4 limbs) ⁎*
- Mechanistic study outcomes
- HR-Quality of Life Questionnaires: EORTC QLQ-C30 and BN20 ‡

* Notes review, † Radiology report, ‡ Patient (carer) reported, ⁎ Trial Office tracked

24. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
N/A	V2.0	07Aug2020		V2.0 was first accepted version of the protocol by REC
SA001	V3.0	13Oct2020	Amy Jones	Addition of wording for eConsenting during the COVID-19 pandemic
SA002	V4.0	14Oct2020	Amy Jones, Puneet Plaha, Sophie Camp	Correction of typos and grammar for clarification. Removal of 6 week and 3 monthly SAE/mortality status check from Stage 1