FUTURE-GB PROSPECTIVE SITE SUMMARY

The FUTURE-GB study is a 2-stage NIHR EME Funded Portfolio trial aiming to assess if the use of extra intra-operative imaging technology - Diffusion Tensor Imaging (DTI) and Ultrasound (US) - during surgical resection can increase deterioration-free survival in patients with newly diagnosed glioblastoma. It is aimed for the trial to be open at Neurosurgery hospitals across the UK where glioblastoma surgery is undertaken.

- Stage 1 is an IDEAL Stage 2b non-randomised cohort, evaluating standard care surgery with the addition of DTI and US imaging during the operation, to inform quality of delivery and standardisation of practices for Stage 2. This stage aims to recruit up to 75 patients over 6-9 months.

- Stage 2 is a prospective, multicentre definitive randomised controlled trial aiming to recruit 357 patients over 27 months, randomising patients to standard care. This Stage has 2 mechanistic sub-studies.

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). *Note: Specifically, the proxy must:* ○ *Be willing and able to give informed consent* ○ *Be able to understand written English to enable completion of trial questionnaires*
Exclusion Criteria	• Midline/basal ganglia/cerebellum/brainstem GB • Multifocal GB • Recurrent GB • Suspected secondary GB • Contraindication to MRI

The trial aims to assess whether additional intraoperative imaging (DTI and NiUS) in addition to standard of care (neuronavigation based on preoperative MRI scan and intraoperative 5-ALA) improves Deterioration Free Survival (DFS) in those having surgery for newly diagnosed glioblastoma.

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).
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)

Those recruited will be followed up for outcomes for up to 24 months after randomisation.

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What is the difference between Stage 1 and Stage 2?
Stage 1 is an IDEAL evaluation, aiming to understand how clinicians use the imaging technologies (DTI and US) during surgery as per study protocol. This Stage is for 6-9 months. This part involves no randomisation and all patients recruited to this stage will have DTI and iUS during surgery.

Stage 2 is the main RCT to answer the trial hypothesis – this stage will include randomisation and the follow-up of patients out to 24 months.

Note - Recruitment of a patient to the trial, will not change any post-surgical treatment pathways.

When will the trial start?
We are hoping (COVID-19) permitting for Stage 1 of the trial to open from October 2020. Once a site completes stage 1 (this will vary due to the number of patients seen at a site), we hope to open Stage 2 and to start randomising patients from spring 2021. It is hoped recruitment to all of the trial will be complete by 2023.

What will the site receive for participating in the trial?

- Medtronic software for performing DTI (if your site does not already have this)
- Brainlab DTI software and also USG integration for performing iUS (where sites have compatible USG)
- Training and mentorship in the use of the technologies used within the trial
- Recruitment activity accrual to an NIHR Interventional Trial

What will a participating site need to undertake?

- Screen potential patients in an online screening log*
- Approach potential patients for consent using an online consent system*
- For stage 2, comply with the trial intervention allocated
- For stage 1, complete trial paperwork at baseline, surgery and hospital discharge
- For stage 2, complete trial paperwork at baseline, surgery, hospital discharge and every 3 months up to 24 months post randomisation*

* You may be able to seek CRN research nurse in undertaking these activities – contact your local CRN if in England, or the devolved nation equivalent. The trial is an NIHR portfolio study.

Who has been involved in the design of the trial?
Clinicians, statisticians, PPI individuals including members of BrainsTrust.

Who is clinically leading the trial?
Professor Puneet Plaha, Ms Sophie Camp and Prof Dipankar Nandi are the neurosurgeons who led the funding application, and would be happy to be contacted to discuss any clinical queries you have regarding the trial.

What do I need to do to register my interest in participating in the trial, or to gain further information?

Please contact Amy Jones, FUTURE-GB Trial Manager on futuregb@nds.ox.ac.uk

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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 (18-75years) 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 post-operative 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