Imaging timing after surgery for glioblastoma - an evaluation of practice in Great Britain: Study protocol

Protocol Preparation:

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STUDY SYNOPSIS

Short title	Imaging timing after glioblastoma surgery
Study ID	INTERVAL-GB
Study description	A UK and Ireland multi-centre retrospective study of imaging practice after surgery for glioblastoma to identify adherence to NICE guidelines, and evaluate imaging strategies utilised.
Primary objective	To assess MRI surveillance practice after surgery for patients with glioblastoma, and delineate if adherence to NICE guidelines improves survival.
Secondary objectives	• To assess adherence to NICE guidelines. • To assess the indications for scanning of patients. • To assess progression-free and overall survival.
Study design	Retrospective study of longitudinal scanning, treatment, and clinical outcomes of glioblastoma patients undergoing surgery and any adjuvant treatment at participating centres, with initial surgery performed between 01/08/2018 and 01/02/2019. Data will be recorded until death or last available date of follow-up.
Study size	456 patients

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1. INTRODUCTION

1.1. Summary

Background

Glioblastoma is the most common primary malignant brain tumour in adults (1), with a median overall survival of 8 months (3). The standard of care comprises of maximal safe surgical resection followed by radiotherapy and concomitant and adjuvant temozolomide (4). Interval magnetic resonance imaging (MRI) plays a role in guiding care for patients with a glioblastoma; it is used for monitoring treatment response, and detecting recurrence/progression.

Optimal timing and frequency of MRI follow up for detecting recurrence in glioblastoma has not been defined. Current practice is based on National Institute for Health and Care Excellent (NICE) consensus guidance (5) as the evidence base for imaging timing is poor (6). A recent survey of UK practice identified a wide variation in imaging schedules (7). The impact of variation in follow-up imaging practice and detection of progression through scheduled or unscheduled imaging is unknown. A recent position statement from the National Cancer Research Institute (NCRI) Brain Tumour group highlighted the lack of evidence and the need for further studies (8).

Aim

The primary aim of this study is to assess MRI monitoring practice after surgery for glioblastoma and evaluate its association with patient outcomes.

Methods

A retrospective, multi-centre audit in newly diagnosed glioblastoma between 01/08/2018 and 01/02/2019 will be conducted. Teams from participating sites consisting of NANSIG and BNTRC collaborators will register and obtain local governance approvals, identify eligible patients, and collect and upload data on a secure online server.

1.2. Background

Gliomas are the most common malignant primary intracranial tumours, accounting for 30% of all brain tumour diagnoses (3, 9). Gliomas are categorised according to the World Health Organisation (WHO) 2016 classification, which includes both histological and molecular characteristics. Of WHO grade 4 gliomas, glioblastoma is the most common in adults accounting for 48.6% of all malignant tumours (3). The incidence of glioblastoma has more than doubled in recent decades, and now has an annual incidence of 5 per 100,000 people, however the reasons behind this are unclear, and may represent an increase in the rate of histological confirmation with surgery and diagnostic accuracy (10, 11). In the UK, almost 2,200 new diagnoses of glioblastoma are made every year (12). Glioblastoma are aggressive, incurable, and have an overall median survival of 8 months, extended to 14-16 months for those treated with standard of care (2, 13). Two-year survival in modern cohorts is 18%, three-year survival is 11%, and five-year survival rate is only 4% (14-16).

The current standard of care for glioblastoma is a combination of surgery, radiotherapy and chemotherapy (2). Gross total resection of all enhancing tumour is associated with increased overall survival (OS) and progression-free survival (PFS) (17, 18). After surgery, patients are followed up with serial surveillance MRI at regular time intervals to detect recurrence. The current National Institute of Health and Care Excellence (NICE) guidelines recommend imaging for glioblastoma to be undertaken at regular intervals, including a post-operative scan to assess extent of resection within 72 hours of surgery, scans at every 3-6 months for the first 2 years after finishing treatment, followed by every 6-12 months for the first 5 years, followed by 1-2 yearly imaging for life. While the guidance specified a tailored approach depending on the patient's clinical status, a recent Cochrane review highlighted that little evidence exists for the optimal imaging strategy (6). Furthermore, a recent survey of neuro-oncology centres in the UK (GIN-CUP study) demonstrated substantial heterogeneity in imaging practices after surgery (7).

The indications for MRI after surgery are:

1. As part of routine follow up (serial)
2. Clinical symptoms suggestive of recurrence (symptomatic) (6, 19)

The James Lind alliance is a priority setting partnership group including patients and clinicians. In 2015 recommendations for what aspects of research in neuro-oncology are most important to patients were devised (Neuro-oncology Top 10). The 2nd priority was to study the effect of interval scanning on

detection of tumour progression and survival, compared with scanning on symptomatic recurrence (20).

From a patient perspective, frequent imaging has been reported to increase anxiety about what it might show - so called 'scanxiety' (21) and claustrophobia is commonly reported by patients undergoing MRI (22). Establishing the most appropriate imaging interval for detecting recurrence could optimise the number of scans received. It is important to establish how necessary it is to have patients under regular follow up, if we should only scan patients if they have recurrent symptoms, or a hybrid approach amalgamating the two. The recent position statement by the National Cancer Research Institute (NCRI) Brain Tumour group emphasised the importance of highly powered studies that examine imaging frequencies after surgery for glioblastoma (23).

2. OBJECTIVES

2.1. Primary objective

To describe MRI surveillance practice after surgery for patients with glioblastoma who have received adjuvant oncology treatment, in accordance with NICE guidelines.

2.2. Secondary objectives

- To assess adherence to NICE guidelines.
- To assess the indications for scanning of patients.
- To assess progression-free and overall survival.

3. STUDY DESIGN

This will be a national, multi-centre, retrospective audit. The study is available to open in all UK and Ireland neurosurgery units and associated oncology services. The study will collect data on consecutive surgical patients with a new histopathological diagnosis of glioblastoma, with surgery between the dates of 01/08/2018 and 01/02/2019. Eligible patients will be identified by local site research teams using existing patient medical and radiological scan records. Since the aim is to assess routine clinical

practice without any change to patient care, this study requires local institutional approval in each participating unit but not NHS research ethics committee (REC) approval.

3.1. Eligibility criteria

Inclusion:

- Surgery (including gross total, subtotal resection and biopsy) between 01/08/18 and 01/02/19
- A new histopathological diagnosis of glioblastoma (according to the 2016 WHO Classification)
- Aged ≥18 years at the time of surgery
- Administration of any adjuvant oncological treatment (radiotherapy and /or chemotherapy)
- MRI follow-up

Exclusion:

- No surgical intervention
- No established histopathological diagnosis
- Follow-up with CT only (MRI contra-indicated)

3.2. Patient identification

Local investigators should use the surgical and neuropathology records, hospital discharge codes, and MDT documents to identify all potentially eligible patients.

3.3. Outcomes

- Imaging intervals and number of MRI scans for patients after surgery.
- Frequency of scheduled (1) and unscheduled (2) MRI scans undertaken in glioblastoma follow-up.
    - A scheduled MRI is defined as an MRI undertaken as part of routine surveillance not performed due to a change in clinical status. If a patient presents and is due a scheduled scan (i.e. has symptoms at a clinic appointment where they are also due to have a scan, this also counts as a scheduled scan).

  - An unscheduled MRI is defined as patient-triggered due to change in symptoms, clinician triggered due to change in symptoms or clinical assessment, and non-brain tumour related (e.g. stroke).
- In cases of suspected progression/pseudoprogression, where a scheduled or an unscheduled scan shows features of progression, which is then assessed afterwards using a follow up scan, the subsequent scan to assess for this would be classified as a scheduled scan.
- Time to disease progression (progression free survival) from surgery. For the purposes of this study, progression is defined as an assessment outcome of disease progression at a multi-disciplinary team (MDT) meeting. If there was no MDT discussion associated with an MRI scan, radiological progression reported in the radiology report is used instead.
- Time to death due to any cause (overall survival) from date of surgery.
- Scanning intervals in adherence with NICE Guidelines, or not in adherence with NICE guidelines.

3.4. Use of primary outcome

Describing the imaging practice in the UK will be helpful in identifying heterogeneity, and establishing the imaging schedules used, which have not been previously explored in the literature. Delineating the progression-free and overall survival of patients scanned in accordance with NICE guidelines will allow us to identify if there is any benefit of regular scanning. Furthermore, we will be able to precisely highlight where progression occurs, which has not been previously described. The results can also be used to inform clinical practice, by validating NICE guidelines, which are currently based on general consensus. Imaging intervals identified in this study can be used for future prospective work, examining the imaging intervals optimised for progression, stratified by patient and histological characteristics, and forming the basis of future trials in imaging, looking at how often patients should be scanned. If there is no survival benefit, this will also inform future qualitative studies examining the perceived benefits of regular follow up imaging in patients with GB.

3.5. Audit standards

The audit criteria are based on current NICE guidance and are the following:

- Offer baseline MRI within 72 hours of surgical resection for glioma.

- Consider a baseline MRI scan 3 months after the completion of radiotherapy for all types of glioma.
- Consider imaging at 3-6 monthly intervals for the first 2 years.
- Consider imaging at 6-12 monthly intervals until 5 years after surgery.

4. STUDY DATA

4.1. Data collection

Data will be collected by the team over a period of 6 months from Monday 15th November 2021 and will end on Friday 27th May 2022. All eligible cases should be included, and local teams should provide a patient flow chart outlining potentially eligible cases from the medical records, and the final number of included patients (Figure 1). Data collection fields are outlined in Appendix A and these relate to routinely available patient, tumour, molecular details, follow up imaging and survival data until date of death, or last follow up (last day of data collection period).

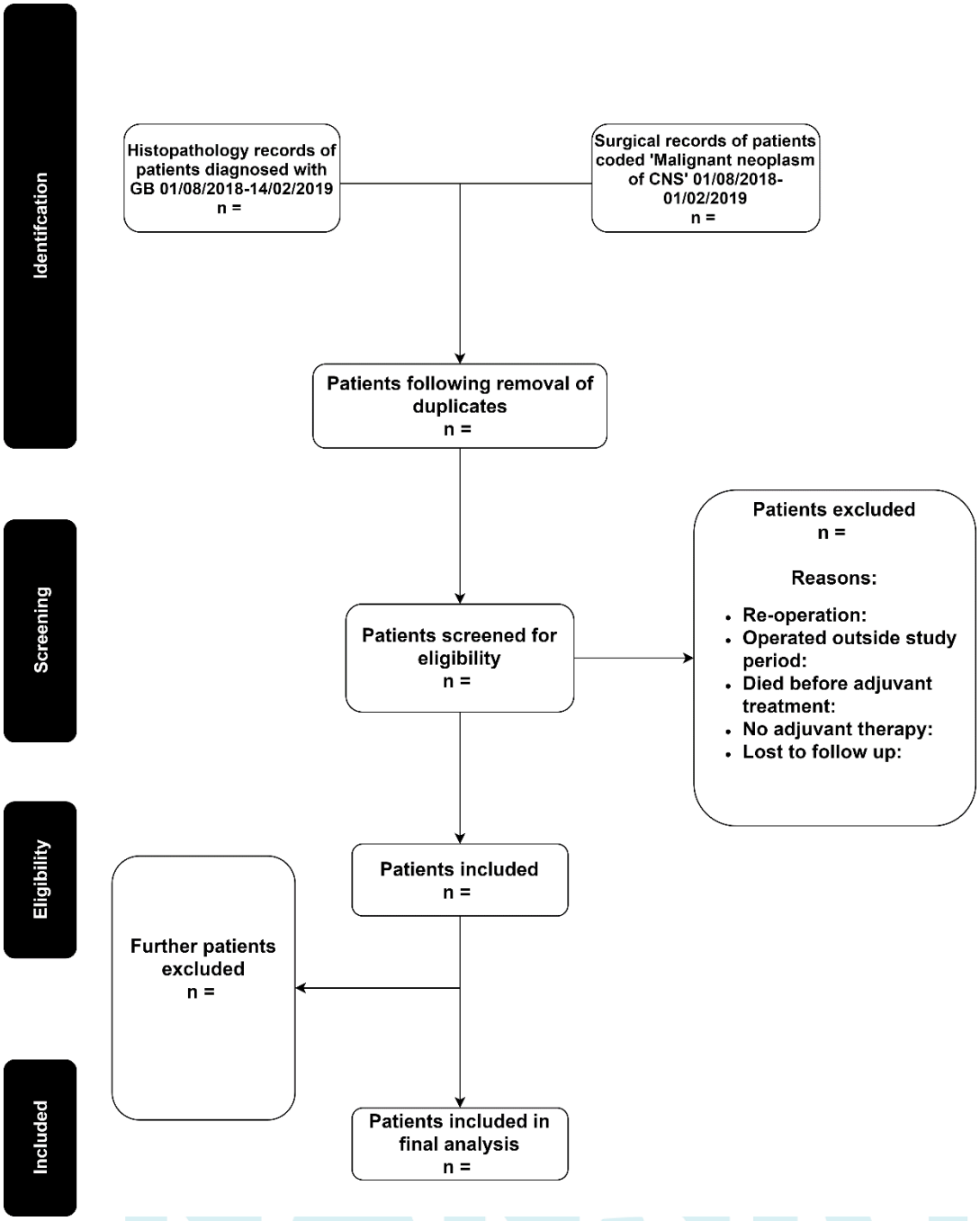

Figure 1. Patient identification flow chart to be completed by all participating centres.

Each neuro-oncology centre will have a local collaborative team formed by the NANSIG regional/hospital leads, a neurosurgical trainee/registrar and a consultant neurosurgeon. The NANSIG regional/hospital project lead must be supported by a trainee and consultant Neurosurgeon, Neuro-

Oncologist, or appropriate healthcare professional to ensure quality of data collected is maintained. The NANSIG regional/hospital lead will act as a local lead for the project and will be responsible for data entry on the online database. Some of the data will require some knowledge of radiological image interpretation, such as tumour location, and if not clear from the radiology report, clarification should be sought from the neurosurgical trainee and reviewed by the consultant neurosurgeon, radiologist, or oncologist if there is still any doubt.

Data is collected locally and submitted to an online server on the secure central database – Castor (25). Local investigators will be given Castor server login details. Any locally collected data must be stored in a secure, locked room that is on-site, or on a password protected NHS hospital computer as per local information governance policy. No patient identifiable information will be uploaded or stored on the Castor database. All patients will have a unique castor ID number traceable to the identifiable patient information only through securely stored forms physically on NHS sites or on password protected NHS computers or servers.

Potential sources of data for case completion will vary for each centre but must include histopathological and surgical records, and may include local hospital online portals, theatre logbook/lists, PACS radiologist reports, patient clinical notes, MDT meetings and MRI scans. Suggestion is to have lists of patients with a histopathology report during the study period, then identify which patients are eligible from there. All student collaborators must specify their data collection strategy and communicate to the steering committee prior to the start of data collection.

4.2. Data Validation and Quality Assurance

Primary investigators and the data collection team will be expected to meet halfway through the data collection phase, and once more at completion of data collection, to identify any issues or concerns. It is the responsibility of the NANSIG local lead to arrange these meetings. Before commencement of data collection, all student collaborators must attend a study meeting, which will cover glioblastoma management, the evidence gap, and the study protocol, and allow students and junior doctors to ask questions before commencement of the study itself.

Each trainee will be involved in the validation of local data collected by the NANSIG collaborator. After data has been completed for a participating centre, any scan results, or MDT results that are categorised as ‘unclear’ by the NANSIG collaborator, will be reviewed, validated, and reasons why

provided by the trainee, to ensure internal validation of data ascertained. Trainee collaborators will also support day-to-day data collection by the local student lead should queries arise.

4.3. Data analysis

Audit standards

For each audit component, we will present the proportion of patients whose imaging schedule was concordant with NICE guidelines. These guidelines will be as follows: the number of patients that receive an MRI scan within 72 hours of surgery, and the number that have follow up scans between 3 and 6 months of finishing treatment. Additionally, we will present these proportions stratified by extent of resection and completeness of multimodal therapy (concurrent and adjuvant temozolomide plus radiotherapy).

Descriptive analysis

Description of study data will be proportions for categorical variables and median with interquartile ranges for continuous variable. The pre-specific subgroup included: patients whose imaging schedule was entirely concordant with NICE recommendations and patients whose imaging schedule had any deviation from NICE recommendations (defined explicitly as having follow up scans every 3-6 months after finishing treatment for the first two years of follow up). Descriptive statistics will also be presented by this subgroup (a group that followed the guidelines and the group that did not have follow up scans every 3-6 months). There are no plans for univariable analyses. For the description of overall and progression-free survival, we will use the Kaplan-Meier estimator to generate the medians by NICE concordant subgroups using the right-censored survival data.

Analytic analysis

The main comparison is to determine whether imaging schedule deviating from NICE recommendations is associated with worse overall survival. We carried out a pilot study to generate estimates for sample size calculation. The pilot included 123 patients from three neurosurgical units showed a median survival of 9.6 months. The proportion of patients who had imaging schedule in accordance with NICE recommendations was 34%. We chose a hazard ratio of 1.35 as our minimally clinically important difference for the study, which roughly equates to 3 months of survival benefit. This margin is similar to the survival benefit of the Stupp trial. Assuming 85% of patients will die during

follow-up, the sample size required based on our pilot data is 456, which would have 80% and 5% type I error rate. We plan to do further subgroup analyses by treatment groups and investigate imaging at different timepoints as a time-varying covariates. Specific analyses are under active development and will be completed before the study period ends.

ETHICS AND DISSEMINATION

4.4. Study registration

The local lead and accompanying research team at each unit are responsible for registering the study as a clinical audit with the clinical audit department of their respective centre, including Caldicott guardian and information governance approval as required. Local leads should send proof of local audit approval to the primary investigators upon registration.

4.5. Local investigator responsibilities

Each local NANSIG student investigator will be responsible for the overall study conduct and compliance with the protocol. The investigator must have read and familiarised themselves with the protocol and the study requirements. All assisting staff (such as supervising consultants, trainees, theatre team members, local clinical audit members) should be informed of the protocol and its availability for review. The local NANSIG student lead at each centre is responsible for the quality of data recorded in the database. Each local NANSIG investigator will be asked to identify what trust systems they will need to access to complete data collection (including access to images, neurosurgical and oncology records) before commencement of the project, at their local centre.

4.6. Confidentiality and data collection

No patient identifiable information will be uploaded or stored on the Castor database. The clinical investigators can only view the records from their own centres. All patient records must be kept in a manner designed to protect patient confidentiality in secure storage with limited access. All data obtained should only be disclosed and used for the purposes of the study only. This must also comply with the requirements of the Data Protection Act 2018 and GDPR according to latest legislation. Training on this is compulsory for local NANSIG student investigators and will be provided. Access to patient data will be restricted to the research team.

4.7. Ownership

Ownership of the complete dataset arising from this study resides with the steering committee (named in the protocol). Proposals to use the data are welcomed and should be directed to the primary investigators.

4.8. Dissemination of results

The results of the study will be presented by the steering committee at national and international meetings, and will be submitted for publication in peer-reviewed journals.

4.9. Authorship eligibility

The INTERVAL-GB study will use a corporate authorship model. The contribution of all investigators will be recognised, and all work (final study results) will be submitted under a sole authorship under the name of the "INTERVAL-GB study collaborative". This will encapsulate BNTRC members under the umbrella term "BNTRC", and NANSIG core committee members involved with the project "NANSIG". The detailed, specific contributions of all authors will be outlined in the appendix of any published material. All students, trainees and consultants will be listed as collaborators. If a journal does not allow a corporate authorship, members of the steering committee will be named authors on behalf of the INTERVAL-GB study collaborative, NANSIG, and the BNTRC in the author by-line.

5.7. Funding

The maintenance of the Castor database is funded by a bursary from the North West Cancer Fund.

5.8. Project Timeline

Data collection will start on Monday 15th November 2021 and will end on Friday 27th May 2022. Below is a chart outlining the study timeline.

	2021										2022											
	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Proposal and protocol drafting																						
Audit application and approval																						
Pilot study in Liverpool, Leeds, and Sheffield																						
Study promotion																						
Centre recruitment																						
Data collection period																						
Data checking																						
Data analysis																						
Data interpretation																						
Presentation of findings																						
Manuscript drafting																						
Manuscript submission																						

6. CONCLUSION

This study will be a national, multi-centre audit collecting data on imaging intervals after glioblastoma surgery.

7. STUDY STEERING COMMITTEE

Name	Organisation	Stage in training	Location	Role
Conor S Gillespie	NANSIG	Medical student	Liverpool	Co-lead for study
Emily R Bligh	NANSIG	Junior Doctor	Glasgow	Co-lead for study
Georgios Solomou	NANSIG	Junior Doctor	Cambridge	Junior doctor coordinator for study, conception of study idea
Melissa Gough	NANSIG	Junior Doctor	Newcastle	Junior doctor coordinator for study
Abdurrahman I Islim	Steering committee	Trainee	Manchester	Trainee co-lead for study
Michael TC Poon	Steering committee	Trainee	Edinburgh	Trainee co-lead for study
Christopher P Millward	BNTA	Trainee	Liverpool	Protocol, study development, recruitment, pilot study (Liverpool).
Ola Rominiyi	Steering committee	Trainee	Sheffield	Protocol, study development, recruitment, pilot study (Sheffield).
Rasheed Zakaria	Steering committee	Trainee	Liverpool	Study development, advice, pilot study (Liverpool).
Paul Brennan	Steering committee	Consultant Neurosurgeon	Edinburgh	Protocol development, advice and guidance throughout.
Stephen Price	Steering committee	Consultant Neurosurgeon	Cambridge	Advice and guidance throughout.
Colin Watts	Steering committee	Professor of Neurosurgery	Birmingham	Advice and guidance throughout, conception of study idea.
Sophie Camp	Steering committee	Consultant Neurosurgeon	Imperial	Advice and guidance throughout.
Shaveta Mehta	Steering committee	Consultant Oncologist	Liverpool	Protocol, oncology specific guidance, data collection proforma development
Thomas Booth	Steering committee	Consultant Neuroradiologist	London	Project conception and feasibility, expert radiology advice throughout, steering advice.
Gerard Thompson	Steering committee	Consultant Neuroradiologist	Edinburgh	Project conception and feasibility, expert radiology advice throughout, steering advice.
Samantha J Mills	BSNR	Consultant Neuroradiologist	Liverpool	Project conception and feasibility, expert radiology advice throughout, steering advice.
Adam Waldman	Steering committee	Professor of Neuroradiology	Edinburgh	Project conception and feasibility, expert radiology advice throughout, steering advice.
Michael D Jenkinson	SBNS	Professor of Neurosurgery	Liverpool	Chief investigator of study, SBNS approval, advice and guidance throughout.

8. APPENDICES

8.1. Appendix A- Required data fields.

Baseline demographics				Information source **Bold= primary source**	Definition
1.	Age at date of surgery (years)	Free field	Required entry	**Patient notes,** surgical theatre logbooks	How old was the patient in years at their operation?
2.	Sex	Male, Female	Required entry	**Patient notes**	What was the sex of the patient?
3.	Date of surgery	Dd/mm/yyyy	Required entry (must be between 01/08/2018 and 01/02/2019)	**Surgical theatre logbooks,** Patient notes/clinic letters,	What was the date the patient had their first operation?
4.	Location	Right, Left, Midline/Bilateral	Required entry	**Radiology scans (i.e. PACS),** clinic letters	The location of the tumour as defined by a consultant radiologist on a pre-operative MRI/CT scan. If report not available, from the consultant Neurosurgeon's clinic letters/operation notes is acceptable.
5.	Main anatomical area involved	Frontal lobe, Parietal lobe, Temporal lobe, Occipital lobe, Limbic lobe, Thalamus and basal ganglia, Corpus callosum, brainstem, Insula	Required entry	**Radiology scans (i.e. PACS)**	The primary area of located tumour as defined by a consultant radiologist on a pre-operative MRI/CT scan. If report not available, from the consultant Neurosurgeon's clinic letters/operation notes is acceptable. If two lobes are mentioned by a surgeon/neuroradiologist i.e 'Frontotemporal', please use the first lobe mentioned. For example, this would be classified as 'frontal lobe'.

6.	WHO performance status prior to surgery	0, 1, 2, 3, or 4	Required entry	**Clinic letters,** surgical logbooks, MDT meetings	Performance status as defined by the consultant neurosurgeon before surgery.
Operative details					
7.	Extent of resection*	Gross total resection (GTR), subtotal (STR)/partial/debulking, biopsy*	Required entry	**Surgical logbooks,** clinic letters	GTR is defined as NO residual enhancing disease (RED) of contrast enhanced tumour as seen on T1-weighted, contrast-enhanced MRI within 72hours post operatively as judged/seen by the neuroradiologist and the neurosurgeon i.e. complete resection. The neuroradiologist and the neurosurgeon will have to reach an agreement. If there is any residual tumour present, it will be classified as a subtotal/partial resection (STR). If a tumour has been incompletely removed (<50%) or labelled as biopsy, it should be considered a biopsy.
8.	IDH status**	Wild-type, mutant, Not done	Required entry	**Pathology report**, clinic letters, MDT meetings	IDH status as defined by a consultant neuropathologist or other appropriate pathology report. A clinical note by the surgeon/treating oncologist outlining specifically the IDH status is also acceptable. Mutant also means IDH positive based on type of staining, and 'IDH negative' will be labelled as 'IDH wild-type' for the purposes of the study as they are the same.
9.	MGMT promoter status	Unmethylated, Methylated, Not done, Test failed, Inconclusive	Required entry	**Pathology report**, clinic letters, MDT meetings	MGMT status as defined by a consultant neuropathologist or other appropriate pathology report. A clinical note by the surgeon/treating oncologist outlining the

		(low levels of methylation)			MGMT promoter status is also acceptable. A 'positive' MGMT status means methylated, and 'negative' unmethylated.
Additional treatments					
10.	Did the patient receive radiotherapy?	Yes, No, not given	Required entry	**Clinic letters**, MDT meetings	Did the patient complete any adjuvant (after surgery) radiotherapy? This is defined by a clinical note by either a consultant oncologist, or other cancer specialist. A clinical note from a consultant neurosurgeon saying the patient has completed radiotherapy is acceptable.
11.	Radiotherapy start date	Dd/mm/yyyy	Appears if answered Yes to previous question; Required entry	**Clinic letters**, MDT meetings	This is defined by a clinical note by either a consultant oncologist, or other cancer specialist. A clinical note from a consultant neurosurgeon saying the patient has completed radiotherapy is acceptable.
12.	Radiotherapy end date	Dd/mm/yyyy	Appears if answered previous question; Required entry	**Clinic letters**, MDT meetings	This is defined by a clinical note by either a consultant oncologist, or other cancer specialist. A clinical note from a consultant neurosurgeon saying the patient has completed radiotherapy is acceptable.
13.	Total Radiotherapy dose (Gy)	Number	Appears if answered previous question; Required entry	**Clinic letters**, MDT meetings	This is defined by a clinical note by either a consultant oncologist, or other cancer specialist. A clinical note from a consultant neurosurgeon saying the patient has completed radiotherapy is acceptable. The number is usually between 54 and 60 Gy for reference.
14.	Radiotherapy fractions	Free field	Appears if answered previous question; Required entry	**Clinic letters**, MDT meetings	This is defined by a clinical note by either a consultant oncologist, or other cancer specialist. A clinical note from a consultant

					neurosurgeon saying the patient has completed radiotherapy is acceptable.
15.	Completed concomitant Temozolomide?	Yes, No	Appears if answered previous question; Required entry	**Clinic letters**, MDT meetings	This is defined by a clinical note by either a consultant oncologist, or other cancer specialist. A clinical note from a consultant neurosurgeon saying the patient has completed temozolomide therapy is acceptable. Concomitant means completed concurrently as the adjuvant radiotherapy.
16.	Adjuvant Temozolomide given?	Yes, No	Required entry	**Clinic letters**, MDT meetings	This is defined by a clinical note by either a consultant oncologist, or other cancer specialist. A clinical note from a consultant neurosurgeon is acceptable. Adjuvant means completed after the radiotherapy treatment, and is commonly started after radiotherapy treatment has finished.
17.	Number of adjuvant Temozolomide cycles completed	1, 2, 3, 4, 5, 6, >6	Required entry	**Clinic letters**, MDT meetings	This is defined by a clinical note by either a consultant oncologist, or other cancer specialist. A clinical note from a consultant neurosurgeon is acceptable. Most patients will have 6 cycles if completing a full course.
18.	Enrolled onto clinical trial?	Yes, No	If yes, additional questions appear asking: 1. Name of trial, and 2. Date of enrolment onto the trial	**Clinic letters**, MDT meetings	This is defined by a clinical note by either a consultant oncologist, or other cancer specialist. A clinical note from a consultant neurosurgeon is acceptable. If a patient has enrolled onto a clinical trial, please provide the name or trial number.
19.	Re-operation for tumour?	Yes, No	Required entry	**Surgical logbooks**, clinic letters, radiology scans	A further operation/surgery with intention of further removal of the tumour, debulking, or

			If Yes, additional question asking for date of re-operation (dd/mm/yyyy).		biopsy. Surgeries for other tumours, ones related to other neurosurgical problems e.g a VP shunt for hydrocephalus, should not be included.
20.	Second line chemotherapy?	Yes, No	Required entry If yes, additional questions asking the agent, number of cycles, dose, and start and end date of chemotherapy.	**Clinic letters**, MDT meetings	Did the patient undergo second line chemotherapy (i.e, chemotherapy treatment for a progression of their tumour)? This is defined by a clinical note by either a consultant oncologist, or other cancer specialist. A clinical note from a consultant neurosurgeon saying the patient has second line chemotherapy is acceptable. This will often be CCNU (Lomustine) or Bevacizumab (Avastin).
21.	Third line chemotherapy?	Yes, No	Required entry If yes, additional questions asking the agent, number of cycles, dose, and start and end date of chemotherapy.	**Clinic letters**, MDT meetings	Did the patient undergo third line chemotherapy (i.e, chemotherapy treatment for a second progression of their tumour)? This is defined by a clinical note by either a consultant oncologist, or other cancer specialist. A clinical note from a consultant neurosurgeon saying the patient has had third line chemotherapy is acceptable. This will often be CCNU (Lomustine), Procarbazine, Temozolomide, or Etoposide.
	Fourth line chemotherapy?	Yes, No	Required entry If yes, additional questions asking the agent, number of cycles, dose, and start and end date of chemotherapy.	**Clinic letters**, MDT meetings	Did the patient undergo fourth line chemotherapy (i.e, chemotherapy treatment for a third progression of their tumour)? This is defined by a clinical note by either a consultant oncologist, or other cancer specialist. A clinical note from a consultant neurosurgeon saying the

					patient has had third line chemotherapy is acceptable. This will often be CCNU (Lomustine), Procarbazine, Temozolomide, or Etoposide.
22.	Re-irradiation?	Yes, No	Required entry If yes, additional questions asking start date, end date, dose and fractionations	**Clinic letters**, MDT meetings	Did the patient undergo further radiotherapy at any point in the clinical journey? This has to have occurred after a previous radiotherapy cycle has been given, and is defined by a clinical note by either a consultant oncologist, or other cancer specialist. A clinical note from a consultant neurosurgeon saying the patient has had re-irradiation is acceptable.
23.	Palliative care?	Yes, No	Required entry If yes, additional question asking date of enrolment in palliative care.	**Clinic letters**, MDT meetings	Has the patient been moved to a palliation treatment strategy at any point? This may mean stopping chemotherapy, radiotherapy or other existing treatments, withdrawing treatment, or other suitable regression from active treatment. This is defined by a consultant neurosurgeon in clinic letters, and/or consultant oncologist when appropriate.
Imaging					
24.	Date of first post-op MRI	Dd/mm/yyyy	Only appears if non-biopsy was selected on extent of resection question; Required entry	**Radiology scans**	This is the first date of MRI that happens after the surgery, and most usually happens within 72 hours of the initial surgery. CT scans should **not** be counted.
25.	Indication	Neurosurgical- assess extent of resection, Radiotherapy planning	Required entry	**Radiology scans**	Indication as listed in the radiology report- this is defined by the consultant neuroradiologist specifically. If the scan is within 72 hours, it

					should be labelled as assess extent of resection, and if it is afterwards, it should be labelled as radiotherapy planning.
MRI Scans (recurring)					
26.	Date of next MRI scan	Dd/mm/yyyy	Required entry	**Radiology scans**	Date of subsequent MRI scan after this.
27.	Scheduled or unscheduled?	Scheduled, unscheduled	Required entry	**Radiology scans**	Defined by the indication on the radiology scans. Please see the objectives for a detailed definition of 'scheduled' and 'unscheduled'. If a radiology report is not available, it may be mentioned by a consultant neurosurgeon/oncologist in the clinic letters. This is acceptable.
28.	If unscheduled, due to clinical symptoms or deterioration?	Yes, No	Appears if answered Unscheduled on previous question; Required entry	**Radiology scans**	Defined in the radiology scans. If a radiology report is not available, it may be mentioned by a consultant neurosurgeon/oncologist in the clinic letters. This is acceptable.
29.	Scan shows	Stable disease, Progressive disease, Pseudoprogression, Unclear	Required entry; if 'Unclear' selected, text-box to prompt collaborator to either copy the report if the report is unclear, or contact the study team if they are unclear how to interpret the scan report to discuss.	**Radiology scans**	Defined in the radiology scan report, by a consultant neuroradiologist specifically. If there is any report of progression (this includes 'mixed disease', it should be coded as progressive disease.
30.	What was the MDT outcome associated with this scan?	No MDT, Stable disease, Progressive disease,	Required entry	**MDT meetings**, clinic letters	Defined as a MDT meeting record confirming the decision that the scan shows progression, and is the outcome of the discussion about the

		Pseudoprogression, Clinical uncertainty			patient. If recorded by one member of the clinical team as 'MDT outcome was progression', this is acceptable.
30.	Another scan?	Yes, No	If yes, MRI form recurs, if no, progress to 'Survival'	**Radiology scans**	Any other MRI head scans that occur after previous scan.
Survival					
31.	Patient still alive?	Yes /No	Required entry If click No, date of death asked	**Clinic letters**, trust systems, NHS Spine	Is the patient recorded as still alive according to the last date of follow up.
32.	Date of death	Dd/mm/yyyy	Required entry	**Clinic letters**, trust systems, NHS Spine	Date of death as reported by Clinic letters, trust systems, or NHS Spine/other pertinent patient outcome registry.
33.	Date of last contact/follow up	Dd/mm/yyyy	Required entry	**Clinic letters**, trust systems, NHS Spine	Date of death as reported by Clinic letters, trust systems, or NHS Spine/other pertinent patient outcome registry.

* In our audit, GTR is defined as NO residual enhancing disease (RED) of contrast enhanced tumour as seen on T1-weighted, contrast-enhanced MRI within 72hours post operatively as judged/seen by the neuroradiologist and the neurosurgeon i.e. complete resection. The neuroradiologist and the neurosurgeon will have to reach an agreement. If there is any residual tumour present, it will be classified as a subtotal/partial resection (STR). If a tumour has been incompletely removed (<50%) or labelled as biopsy, it should be considered a biopsy.

**IDH status- Wild type will also mean IDH positive based on type of staining, and 'IDH negative' will be labelled as 'IDH mutant' for the purposes of the study they are the same.

8.2. Appendix B- Neurosurgical centres and local data collection groups

Neurosurgical Centre	Medical School	NANSIG Collaborators
Aberdeen Royal Infirmary	University of Aberdeen	
Addenbrookes	University of Cambridge	
Beaumont Hospital	Royal College of Surgeons in Ireland	
Charing Cross Hospital	Imperial College London	
Cork University Hospital	University College Cork	
Derriford Hospital	Plymouth University	
Essex Neurological Centre	Bart's and The London	
Hull Royal Infirmary	University of Hull	
James Cook University Hospital	Newcastle University/University of Sunderland	
John Radcliffe Hospital	University of Oxford	
King's College Hospital	King's College London	
Leeds General Infirmary	University of Leeds	
Ninewells Hospital	University of Dundee	
Princess Royal Hospital		
Queen's medical centre (QMC) University Hospital	University of Nottingham	
Queen's Hospital		
Royal Hallamshire Hospital	University of Sheffield	
Royal London Hospital	Bart's and The London	
Royal Preston Hospital	University of Central Lancashire	
Royal Stoke, North Midlands	Keele University	
Royal Victoria Hospital	Queen's University Belfast	
Royal Victoria Infirmary	Newcastle University	
Salford Royal Hospital	University of Manchester	
Southampton General Hospital	University of Southampton	
Southern General Hospital	University of Glasgow	
Southmead Hospital	University of Bristol	
St Bartholemew's and Royal London Hospital	Bart's and The London	
St George's Hospital	St George's University of London	
The National Hospital for Neurology and Neurosurgery	University College London	
The Princess Royal Hospital	University of Brighton	
The Queen Elizabeth Hospital	University of Birmingham	
The Walton Centre	University of Liverpool	
University Hospital of Wales	Cardiff University	
Walsgrave Hospital	University of Warwick	
Western General Hospital	University of Edinburgh	

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