

Protocol for the Tessa Jowell BRAIN MATRIX Platform Study

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BRAIN MATRIX

1 **Protocol for the Tessa Jowell BRAIN MATRIX Platform Study**

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22 **Abstract**

23 **Introduction**

24 Gliomas are the most common primary tumour of the central nervous system (CNS), with an estimated
25 annual incidence of 6.6 per 100,000 individuals in the USA and around 14 deaths per day from brain
26 tumours in the UK. The genomic and biological landscape of brain tumours has been increasingly defined
27 and, since 2016, the WHO classification of tumours of the CNS incorporates molecular data, along with
28 morphology, to define tumour subtypes more accurately. The Tessa Jowell BRAIN MATRIX Platform (TJBM)
29 study aims to create a transformative clinical research infrastructure that leverages UK NHS resources to
30 support research that is patient centric and attractive to both academic and commercial investors.

31 **Methods and analysis**

32 The TJBM study is a programme of work with the principal purpose to improve the knowledge of glioma
33 and treatment for glioma patients. The programme includes a platform study and subsequent
34 interventional clinical trials (as separate protocols). The platform study described here is the backbone
35 data-repository of disease, treatment and outcome data from clinical, imaging and pathology data being
36 collected in glioma patients from secondary care hospitals. The primary outcome measure of the platform
37 is time from biopsy to integrated histological-molecular diagnosis using whole genome sequencing and
38 epigenomic classification. Secondary outcome measures include those that are process-centred, patient-
39 centred and framework-based. Target recruitment for the study is 1000 patients with interim analyses at
40 100 and 500 patients.

41 **Ethics and dissemination**

42 The protocol was approved by West Midlands - Edgbaston Research Ethics Committee. Participants will be
43 required to provide written informed consent. The results of this study will be disseminated through
44 national and international presentations and peer-reviewed publications.

45 **Trial registration number**

46 ClinicalTrials.gov Identifier: NCT04274283; 18-Feb-2020

47 ISRCTN 14218060; 03-Feb-2020

48

49 **Strengths and limitations of this study**

- 50 • The TJBM study is a programme of work, which will improve the knowledge of glioma, and
51 treatment for glioma patients.
- 52 • This platform study is a backbone data-repository of disease, treatment and outcome data from
53 clinical, imaging and pathology data
- 54 • The TJBM study will aim to provide rapid and accurate molecular diagnosis, a network of clinical
55 hubs with robust protocols for the collection, processing, analysis and storage of tissue, images,
56 and clinical and quality of life data
- 57 • Gliomas occur at all ages and their specific subtype is difficult to predict preoperatively, therefore,
58 the patient population eligible for the study is broad but currently excludes <16-year-old patients

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59 **Introduction**

60 Gliomas are the most common primary tumour of the central nervous system (CNS), with an estimated
61 annual incidence of 6.6 per 100,000 individuals in the USA (1), which is predicted to rise to 22/100,000 by
62 2035 (2). In 2016, there were 5,250 deaths from brain tumours in the UK i.e., 14 deaths per day (2).
63 Malignant CNS tumours hold the poorest prognosis, and are responsible for the highest estimated number
64 of years of potential life lost (mean 20 years) amongst all cancers (3) and survival trends have remained
65 generally static in comparison to other cancers (4).

66 Gliomas have traditionally been divided into low grade glioma (LGG; WHO I-II) and high-grade glioma (HGG;
67 WHO III-IV) based on integrated classic histological features and molecular biomarkers (5). LGG have an
68 indolent course with patients commonly surviving a decade after diagnosis (6). However, the natural
69 history of many WHO Grade II LGG is progression to HGG. Approximately half of all newly diagnosed
70 gliomas are classified as glioblastoma (GB; WHO IV), the most malignant type of brain cancer. Currently,
71 the GB annual incidence is 3.2 per 100,000 population in the USA. This tumour occurs more frequently with
72 advancing age; ranging from 0.4 per 100,000 population aged 20–34 years, to over 15 per 100,000
73 population aged 75–84 years (1). It is widely recognized that elderly populations are rapidly increasing
74 globally and this will have a significant impact on the burden of GB disease. Despite this, most studies still
75 focus on patients younger than 65 years.

76 The current gold standard treatment for newly diagnosed GB is surgical gross total resection (GTR),
77 followed by radiotherapy with concomitant and adjuvant temozolomide. The aim of treatment is to delay
78 tumour progression and extend overall survival (7). Despite decades of refinement, this approach results
79 in a median survival time of only 12-14 months.

80 Over the last 20 years the genomic and biological landscape of brain tumours has been increasingly defined,
81 refining previous classification systems, unravelling intra- and inter-tumoural heterogeneity and
82 progression, identifying drug targets and potential therapeutic strategies, and better characterising
83 challenges to therapies, such as the blood brain barrier (BBB) and mutational escape. In 2016, the WHO
84 published its classification of tumours of the CNS (5), which for the first time used molecular data, along
85 with morphology, to define tumour subtypes more accurately. This stratification integrated a combination
86 of specific genetic and epigenetic biological characteristics that are changing rapidly as our knowledge
87 evolves (8). In recognition of this rapid evolution of knowledge, 'cIMPACT-NOW' (Consortium to Inform
88 Molecular and Practical Approaches to CNS Tumor Taxonomy – Not Official WHO) (9) was created, with the
89 new WHO 2021 classification representing a consensus opinion based on new insights into the molecular
90 definition of brain tumours from this collaboration (10). As analytical technologies evolve and become
91 more affordable, genome-wide analyses combined with other so-called 'omics' data will lead to further
92 refinement of tumour classification with meaningful impacts on prognosis and choice of therapy. This is
93 the motivation for the TJBm study, which will adopt whole-genome sequencing (WGS) and epigenomic
94 analysis of tumour samples.

95 The TJBm study aims to create a transformative clinical research infrastructure that leverages NHS
96 resources to support research that is patient centric and attractive to both academic and commercial
97 investors. Our approach will be holistic and flexible so that it can rapidly adapt to scientific advances and
98 rigorously evaluate new drugs and technologies. To achieve this, it will establish a research-active network
99 of clinicians and scientists who are well supported by an innovative trial infrastructure to deliver the
100 following:

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- 101 • Rapid and accurate molecular diagnosis ensuring precise classification of tumours and identifying
102 subsets of patients suitable for targeted therapy, by building on the legacy of the 100,000
103 Genomes Project (11).
- 104 • A network of clinical hubs resourced to maximise patient recruitment and collect tissue and data.
- 105 • Robust protocols for the collection, processing, analysis and storage of tissue, images and clinical
106 and quality of life (QoL) data, building on existing infrastructure such as UK Biobank (12), Medical
107 Research Council (MRC) Brain Banks Network (13), and the CRUK PEACE study (14).
- 108 • High-quality biological samples that are fully clinically and radiologically annotated facilitating
109 further biological and radiological research.
- 110 • Links to national and international clinical and scientific infrastructure and networks (15); e.g.,
111 Genomics England (GEL), European Network for Rare adult solid Cancer (EURACAN) (16), SIOP-E
112 Brain Tumour Group, and National Cancer Research Institute (NCRI) Groups.
- 113 • Access to novel and repurposed drugs and technologies through collaborative partnerships with
114 industry and early phase trials hubs and the structural genomics consortium (www.thesgc.org), to
115 develop novel trials, within and outside, the TJBM infrastructure for testing of therapeutic
116 strategies, including novel agents. As such therapeutic clinical trials will be developed using this
117 infrastructure to maximise efficiency in introducing and rigorously evaluating novel interventions.
118 These will be separate protocols to the TJBM study.
- 119 • Long-term sustainability through delivery of clinically and scientifically meaningful outcomes,
120 leveraged investigator-led research grants and an established cost-recovery model for biobanking
121 (17).

122 **Methods and analysis**

123 **Study design**

124 The TJBM study is a programme of work the principal purpose of which is to improve the knowledge of
125 glioma and treatment for glioma patients. The programme will include a platform study and subsequent
126 interventional clinical trials (as separate protocols); Figure 1. This platform study, is the backbone data-
127 repository of disease, treatment and outcome data from clinical, imaging and pathology data to be
128 collected in glioma patients from secondary care hospitals. Figure 2 shows an overview of the platform's
129 study schema.

130 The study aims to recruit 1000 patients within the UK over 5 years with participants followed up for up to
131 5 years. An initial 10 UK centres were opened to the TJBM study, as listed in Supplementary Appendix 1,
132 although further centre expansion is planned. The Standard Protocol Items: Recommendations for
133 Intervention Trials (SPIRIT) checklist is provided as Supplementary Appendix 2 (18). The World Health
134 Organization (WHO) Trial Registration Data Set is provided in Supplementary Appendix 3.

135 **Patient and public involvement**

136 Patient and public involvement and engagement (PPIE) has been integral to this study from its inception.
137 Our patient and public advisors, Helen Bulbeck and Peter Buckle, co-developed the TJBM study by
138 reviewing and refining the protocol and the participant-facing documents. They have provided input into
139 the patient-reported outcome measures and have guided messaging about the study for the community.
140 As members of the Study Management Group (SMG; Supplementary Appendix 1) they continue to assess
141 study conduct, and will contribute to the interpretation and dissemination of study findings through the

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142 PPIE dissemination strategy. This will include presentation of the study findings to identified audiences, the
143 best channel for reach, when to communicate, messaging and sensitivities.

144 **Patient selection**

145 Patients aged ≥ 16 years with newly diagnosed suspected WHO Grade II-IV glioma, (as evidenced
146 radiologically) suitable for a diagnostic or therapeutic surgical procedure resulting in a tumour sample
147 matched to a blood sample or with progression with known WHO Grade II-IV glioma will be eligible.

148 Patients with primary spinal cord tumours, who are receiving active treatment of other malignancy, have
149 contraindications to magnetic resonance imaging (MRI) and/or without standard of care imaging available,
150 will be excluded.

151 Newly diagnosed patients with suspected WHO Grade II-IV glioma who are subsequently found to have a
152 WHO Grade I tumour or non-brain tumour are expected to be a rare occurrence. If this event occurs:

- 153 • If it is confirmed as a Grade I tumour, then the patient will remain eligible for the study and will
154 continue to be followed up in accordance with the protocol.
- 155 • If it is confirmed as a non-brain tumour, then the patient will not remain on the study and no
156 further follow-up data will be collected.

157 All patients must be able to provide written informed consent for the study.

158 **Consent**

159 Supplementary Appendix 4 contains exemplar informed consent forms (ICF), with Supplementary Appendix
160 5 the patient information sheets (PIS) and lay summary for the study. The investigator or an appropriately
161 trained delegate must obtain written informed consent for each patient prior to performing any study
162 related procedure. Remote Consent for platform entry is permitted by telephone or video consultation
163 instead of face-to-face consultations.

164 In addition, to consenting to join TJBM, patients will be required to provide agreement for:

- 165 • The collection and analysis of biological samples (e.g., tumour, blood), including access to existing
166 and future samples.
- 167 • The collection of relevant clinical information, including imaging and pathology.
- 168 • The return of clinically relevant results back to the referring clinician.
- 169 • The use of, and sharing of data, for research, teaching, commercial and scientific purposes,
170 including data sharing through The Brain Tumour Charity's BRIAN (the Brain tumouR Information
171 and Analysis Network) database (19).
- 172 • The collection of different aspects of health data from the NHS and other Department of Health
173 organisations (in addition to medical records) for longitudinal analysis and follow-up.
- 174 • The use of clinical data to identify potential clinical trials or other research that they may benefit
175 from.
- 176 • The sharing of samples for other ethically approved research projects.

177 In addition, and in line with GEL processes and studies such as the 100,000 Genomes Project, optional
178 consent will be taken as to whether the patient would like to receive feedback about the evidence of
179 inherited diseases (both underlying the cause of the cancer and non-cancer causes).

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180 For centres submitting tumour tissue for WGS through the standard of care (SoC) NHS Genomic Medicine
181 Service (GMS) pathway in England, an additional GEL consent step is currently required to confirm consent
182 at the point of referral for the patient's clinical indication. This additional GEL consent step is performed
183 electronically or on paper and can be completed over the phone.

184 **Platform assessments and schedule of events**

185 Platform entry requires baseline clinical data, NIH Stroke Scale (20), weight, and WHO Performance Status
186 to be recorded, and then performed again at start and end of concomitant therapy, start and end of
187 adjuvant therapy, further surgery and during the five-year follow-up period.

188 In addition, QoL questionnaires will be completed at the initiation of concomitant therapy, initiation of
189 adjuvant therapy, further surgery and during follow-up. The QoL booklet includes EQ-5D-5L (21), EORTC-
190 QLQ-c30 (22), Patient Concerns Inventory (PCI) (23), Patient Global Impression of Change (PGIC) (24), and
191 Clinician Global Impression of Change (25).

192 The schedule of events is included in Supplementary Appendix 6.

193 **Platform study outcome measures**

194 The primary outcome measure of the platform is time from biopsy to integrated histological–molecular
195 diagnosis (TTMD) as defined as the difference (in days) between date of biopsy and date of WGS and
196 epigenomic classification.

197 Secondary outcome measures include those that are process-centred, patient-centred, and framework-
198 based.

199 Process-centred secondaries include: time to completion of each node of tissue and imaging pathway;
200 tumour and biological sample(s) quality control (QC) status; imaging QC status, and; inter-rater agreement
201 of response assessment in neuro-oncology (RANO) (26).

202 Patient-centred secondaries include: extent of surgical resection; overall survival time (OS); intracranial
203 progression-free survival time (PFS); QoL scores; type of interventions received; type of complications from
204 treatments (standard of care) received, and; concordance between initial local radiological diagnosis, local
205 pathological diagnosis, and integrated histological-molecular diagnosis.

206 Research framework-based secondaries include: samples and images centrally stored; targetable
207 mutation(s) identified; post-mortem sampling consent status and sample collection confirmation, and;
208 number of applications to, and outputs resulting from data repository (including trial proposals both within
209 and outside of the TJB network).

210 **Statistical analysis plan**

211 The target sample size for the study is 1000 patients. The primary remit of TJB network study is to establish a
212 central data repository that will support the development and delivery of precision medicine for all glioma
213 patients in the UK. As such, there is no statistical basis behind the choice of target sample size, but this
214 number will allow robust assessment of feasibility and subgroup analyses. Sample size for any clinical trials
215 that are subsequently linked to the platform will be based on statistical justification.

216 A formal interim analysis of the primary outcome measure (TTMD) and any relevant secondaries will be
217 performed after registration and diagnosis of the first 100 patients and after 500 patients. There are no

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218 formal stopping rules. Formal analyses of all study outcome measures will be performed once the study
219 has completed recruitment (target 1000 patients) and completed the follow up for all registered patients.

220 The analysis of TTMD will essentially be descriptive. The median TTMD will be reported overall and for each
221 centre, together with the proportion of patients achieving TTMD within 28 days. Graphs of the change in
222 both these summary statistics over time will be used to explore if TTMD changes during the course of the
223 study. All estimates will be accompanied by 95% confidence intervals (CI). The time to completion of each
224 node of tissue and imaging pathway will be reported as medians together with 95% CI, both overall and for
225 each centre. Swimmer plots will be used to depict overall and node level timings for each patient.

226 For each type of tumour and biological sample, the proportion of sample passing QC and successfully
227 undergoing WGS and EC will be reported with 95% CI and similarly for the imaging QC outcome measures.
228 Inter-rater agreement of RANO will be assessed through Kendall's coefficient of concordance.

229 Extent of surgical resection is evaluated from the post-operative MRI scan and is categorised as either;
230 closed biopsy, open biopsy, debulking <50%, subtotal resection 50-90%, near total resection 90-<100%,
231 gross total resection 100%. The extent of surgical resection will be reported as the proportion falling into
232 each category together with 95% CI.

233 OS is defined as the time from date of diagnosis to the date of death with patients who are alive at the
234 time of analysis censored at the date last seen in clinic. Intracranial PFS time is defined as the time from
235 date of registration to the earliest of date of intracranial progressive disease or death from disease. The
236 date of an event is defined as the earliest confirmation of progression by radiological assessment, clinical
237 symptoms or multidisciplinary team (MDT). Patients without progression at the time of analysis will be
238 censored at the date last seen in clinic.

239 OS and intracranial PFS will be analysed and plotted using the Kaplan-Meier method. Median times with
240 corresponding 95% CI will be reported together with rates at 1, 2 and 5 years. Multivariable survival
241 regression modelling will be used to explore prognostic factors, including, but not limited to, WHO 2021
242 classification, age, tumour volume, stage, methylation and mutation status.

243 Longitudinal measures of QoL will be generated from the QoL questionnaire according to the
244 questionnaire-specific algorithms for scoring. The analysis of longitudinal QoL scores will essentially be
245 descriptive. For each of the multiple QoL scores generated from the different questionnaires, the means,
246 medians or proportions (as appropriate) will be plotted over time together with 95% CI. These repeated
247 measures over time may be modelled, if appropriate, with a linear or more flexible mixed model that takes
248 account of the within-subject correlation and will allow exploration of factors associated with the outcome.

249 Details of the type of intervention received and complications (e.g., surgical wound infection) relating to
250 standard of care treatments received will be monitored and recorded throughout the follow-up period and
251 reported descriptively as frequencies and associated percentages. In relation to initial local logical
252 diagnosis, local pathological diagnosis and integrated histological-molecular diagnosis, any difference
253 between the tiers of diagnoses will be highlighted and categorised as: discordant; agreed; refined and
254 reported descriptively as frequencies and associated percentages.

255 Confirmation of central storage of images and material, relevant targetable mutations identified by WGS
256 and epigenomic classification, and receipt of post-mortem consent forms with confirmed central storage
257 of samples will be recorded and reported descriptively.

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258 Planned subgroup analyses of outcome measures include: IDH mutated and wildtype tumours; residual
259 enhancing disease (RED; none, operable, inoperable); methylated and un-methylated tumours; age groups;
260 types of diagnosis (WHO 2021 criteria only, epigenetic classification only, WGS analysis only, integrated
261 diagnosis comprising all three); performance status; sex, and; biomarkers that emerge during the study
262 (either discovered in the TJBM study or reported in the literature) that are deemed relevant after review
263 by the Scientific Advisory Board (SAB).

264 **Biological samples**

265 **Sample collection**

266 Biological samples will be collected at each participating site following agreed protocols and guidance from
267 the central biospecimen coordination centre (Oxford BRAIN MATRIX Laboratory). The aim is to build as
268 much as possible on existing GEL infrastructure and pathways. The funded pathway is represented in Figure
269 3.

270 Fresh tissue for TJBM must be frozen in liquid nitrogen and stored until shipment to the Oxford BRAIN
271 MATRIX Laboratory. Matched 'germline' DNA from white blood cells is required for the detection of
272 somatic variants for paired blood/tumour WGS. This should be collected as per standard GEL protocols.
273 Ideally, it should be collected prior to or at the time of first surgery. The blood sample(s) must be shipped
274 together with the frozen tissue of the patient to the Oxford BRAIN MATRIX Laboratory.

275 For patients who are not undergoing surgery and have available tumour samples from previous tumour
276 surgery, blood should be collected and sent to the Oxford BRAIN MATRIX Laboratory along with their
277 tumour samples.

278 For participants unable to donate a blood sample, a saliva sample is an acceptable alternative.

279 Where possible, it is intended to collect blood samples for liquid biopsies of the tumour (e.g., tracking
280 circulating tumour cell free (cft)DNA within the blood). Samples should ideally be collected at the time of
281 operation, before the neurosurgeon performs any incision, ideally in theatres or the anaesthetics room just
282 before any biopsy. Where feasible further blood samples should be collected at the following key treatment
283 milestones:

- 284 1. At first post-operative MRI
- 285 2. Initiation of concomitant therapy (if applicable).
- 286 3. The end of concomitant therapy (if applicable).
- 287 4. Initiation of adjuvant therapy (if applicable).
- 288 5. The end of adjuvant therapy (if applicable).
- 289 6. The time of objectively measured progression.
- 290 7. During the palliative phase if a post-mortem has been agreed.

291 Where cerebrospinal fluid (CSF) is available for the patient, this should also be submitted.

292 Participating sites should follow the CRUK PEACE study protocol for post-mortem neurological tissue
293 donation. The aim of post-mortem tissue donation is to enable research into:

- 294 1. The clonal evolution of the glioma after emergence of therapy resistance.
- 295 2. Tumour host-interaction at the whole brain level.
- 296 3. The effect of radio-chemotherapy on normal brain.

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297 4. The interaction between the glioma and non-CNS organs (e.g., immune system in the cervical
298 lymph nodes).

299 **Sample analyses**

300 Matched tumour/blood samples collected at first surgery are the most important samples of the TJB
301 study as these determine the initial integrated histological-molecular diagnosis. Following histological QC,
302 the Oxford BRAIN MATRIX Laboratory will perform DNA extraction and QC; an aliquot will be sent to the
303 Illumina Centre in Cambridge for WGS, and one used for EPIC methylation array at the Wellcome Trust
304 Centre for Human Genetics in Oxford. Remaining DNA and unused tissues will be stored at the BRAIN
305 MATRIX Biorepository.

306 Raw WGS data will be maintained in the GEL Data Research Environment, where it can be accessed and re-
307 analysed by data scientists at the submitting NHS Genomic Laboratory Hub or any qualifying TJB
308 approved researcher. Sample data not generated by GEL will be consolidated in established bioinformatics
309 hubs of the University of Oxford (Big Data Institute/Weatherall Institute for Molecular Medicine).

310 Data files on the Illumina 850k EPIC BeadChip analysis will be uploaded to the 'Heidelberg Classifier' hub at
311 the German Cancer Centre in Heidelberg (27). This will generate an automated classifier report which will
312 be stored at the Oxford BRAIN MATRIX Lab. Raw array data will be made available via the Oxford BRAIN
313 MATRIX Laboratory.

314 Matched histological sections will be digitised at the Oxford BRAIN MATRIX Laboratory resulting in linked
315 genomic data, which will initially be stored in Oxford. As the study evolves, we will aim to capture digital
316 histological data from the material kept at the local neuropathology centre. The Oxford BRAIN MATRIX hub
317 is working with CRUK-established data visualisation platforms, such as those developed for S:CORT
318 (Colorectal Cancer) (28) and based on international open access platforms (such as cBioPortal (29)).

319 The BRAIN MATRIX neuropathology and genomics team will generate an integrated report (histology, WGS,
320 Heidelberg Classifier) for each case in consultation with the local neuropathology team. The primary BRAIN
321 MATRIX report will comprise the formal routine GEL WGS report (germline and tumour) and Heidelberg
322 Classifier report and integrate this with the histological and molecular report issued by the recruiting site.
323 It is anticipated that a local histological and molecular diagnosis using immunohistochemical surrogate
324 markers and targeted genetic analyses will be available before WGS and Illumina EPIC BeadChip data are
325 returned to the Oxford BRAIN MATRIX Lab. When available, the BRAIN MATRIX neuropathology and
326 molecular genetics team will conduct a virtual MDT with the referring site to ensure all relevant information
327 will be incorporated in the final BRAIN MATRIX diagnostic report. Variant calling and classifier outputs will
328 be determined by the practice at the GEL/Illumina Centre and the version of the Heidelberg Classifier
329 algorithm active at the time of sample analysis.

330 Where relevant germline data is identified, local sites should facilitate local genetic referral as per other
331 GEL study protocols.

332 **Imaging data**

333 Pseudo-anonymised longitudinal clinical imaging (MRI) for each patient will be collected and stored at a
334 central imaging hub overseen by the Edinburgh Imaging Hub. Disease response assessment will be
335 performed by practicing UK neuro-radiologists with a neuro-oncology interest via the Edinburgh Imaging
336 Platform and additional analyses undertaken through the University of Edinburgh image analysis laboratory
337 with permitted partners.

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338 As per patient standard of care, it is expected that imaging will be performed pre- and post-operatively, for
339 radiotherapy planning, following any chemoradiation, and as per follow-up determined by the managing
340 MDT and/or if clinical concerns are raised regarding disease progression.

341 Pragmatic MRI protocols will be conducted as per standard of care MRI protocols and timing following
342 diagnosis and as such will be informed by the National Institute for health and Care Excellence (NICE)
343 guidelines from 2018 (30), in line with the recent British Society of Neuroradiologists (BSNR) imaging
344 guidance (31), which is itself an implementation of the Brain Tumour Imaging Protocol proposed by
345 Ellingson *et al.* (32). Where additional advanced imaging is performed this is also encouraged to be
346 submitted to the Edinburgh Imaging Hub and will be catalogued to permit any relevant subsequent
347 analysis. Biopsy location imaging should also be submitted, and standard operating protocols for the major
348 neuro-navigation systems followed. Radiotherapy planning imaging will also be submitted.

349 The RANO assessments will be performed through a secure web portal provided by QMENTA Inc. There
350 will be an ongoing 10% re-read to assess inter-rater agreement. It is anticipated that RANO reports will be
351 provided within 2 weeks (10 working days) of successful transfer of imaging requiring assessment. RANO
352 reports will categorise response where possible into Complete Response (CR), Partial Response (PR), Stable
353 Disease (SD) or Progressive Disease (PD). In cases of diagnostic uncertainty, potential or provisional
354 outcomes may be recorded, allowing progression events to be backdated to the correct time point should
355 subsequent imaging be confirmatory.

356 **Adverse events reporting**

357 There are no study treatments within the TJBM study. Blood sampling and completion of QoL
358 questionnaires are the only procedures that patients undergo additional to usual care. Therefore, it is not
359 anticipated that there will be adverse events related to participation in this study. Only severe adverse
360 events (SAEs) relating to those additional procedures will be reported as per Common Terminology Criteria
361 for Adverse Events (CTCAE) version 4 (33) and as defined in Supplementary Appendix 7. The reporting
362 period is from the date of informed consent to death.

363 **Data management**

364 Case report forms will be entered online via a secure web-based portal. Authorised staff at sites will require
365 an individual secure login username and password to access this online data entry system. Paper CRFs will
366 be available for backup only and must be completed, signed/dated and returned to the BRAIN MATRIX
367 Study Office by the investigator or an authorised member of the site research team. Data reported on each
368 CRF should be consistent with the source data or the discrepancies should be explained. If information is
369 not known, this must be clearly indicated on the CRF. All missing and ambiguous data will be queried. All
370 sections are to be completed.

371 All study records must be archived and securely retained for at least 25 years. No documents will be
372 destroyed without prior approval from the sponsor, via the central Study Office. On-site monitoring will be
373 carried out as required following a risk assessment and as documented in the Quality Management Plan.
374 Any monitoring activities will be reported to the central BRAIN MATRIX Study Office and any issues noted
375 will be followed up to resolution. BRAIN MATRIX will also be centrally monitored, which may trigger
376 additional on-site monitoring. Further information regarding data management is provided in the study
377 protocol.

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378 The CRCTU will hold the final study dataset and will be responsible for the controlled sharing of anonymised
379 data with the wider research community to maximise potential patient benefit while protecting the privacy
380 and confidentiality of study participants. Data anonymised in compliance with the Information
381 Commissioners Office requirements, using a procedure based on guidelines from the Medical Research
382 Council (MRC) Methodology Hubs, will be available for sharing with researchers outside of the trials team
383 within 12 months of the primary publication.

384 **Trial organisation structure**

385 The University of Birmingham will act as single sponsor to this multi-centre study: Support Group, Aston
386 Webb Building, Room 119, Birmingham, B15 2TT. Email: researchgovernance@contacts.bham.ac.uk). The
387 study is being conducted under the auspices of the CRCTU, University of Birmingham according to their
388 local procedures.

389 The Chief Investigator, Co-investigators, Trial Management Team Leader, Senior Trial Coordinator, Trial
390 Coordinator, Lead and Trial Statistician, Trial Monitor and patient representatives will form the Study
391 Management Group (SMG; current membership is listed in Supplementary Appendix 1). The SMG will be
392 responsible for the day-to-day conduct of the TJBm study, meeting at regular intervals (e.g., at least every
393 three months), or as required, usually by teleconference. They will be responsible for the set-up,
394 promotion, on-going management of the study, the interpretation of the results and preparation and
395 presentation of relevant publications.

396 Selected findings of clinical significance will be presented to the Scientific Advisory Board (SAB), which as a
397 minimum will include the Chief Investigator, an oncologist, a pathologist, and a molecular biologist for a
398 combined review of the molecular findings in context. The SAB may suggest amendments that will be
399 incorporated into a SAB Report, which will be sent to the Executive Oversight Committee (EOC); current
400 SAB and EOC membership is listed in Supplementary Appendix 1. Possible re-testing/further testing may
401 be required, as a result of SAB feedback. Guided decision-making tools that review results in the context
402 of the literature and clinical experience will be piloted within the SAB. The SAB will also evaluate research
403 and study proposals, manage data/tissue requests, and will report back to the EOC regarding any proposals
404 or changes which they may suggest.

405 The overarching remit of the EOC is to mandate, including timeframe and deliverables, the responsibility
406 of the SAB and to take responsibility of horizon scanning to enable the incorporation of new interventional
407 arms. They will oversee the overall study management of both the platform and any standalone
408 interventional trials. They will also liaise with other trial units and pharma stakeholders as well as funders,
409 charities, study sponsors, and policymakers and liaise with the BRIAN team. A quarterly EOC Report will be
410 disseminated to all stakeholders that will demonstrate the performance metrics of each clinical site. In
411 addition, the use of all samples given to external researchers via the SAB will be included in the report.

412 **Confidentiality**

413 Confidential information collected during the study will be stored in accordance with the General Data
414 Protection Regulation (GDPR) 2018. As specified in the patient information sheet (PIS) and with the
415 patients' consent, patients will be identified using only their date of birth and unique study ID number.
416 Authorised staff may have access to the records for quality assurance and audit purposes. The BRAIN
417 MATRIX Study Office maintains the confidentiality of all patients' data and will not disclose information by
418 which patients may be identified to any third party other than those directly involved in the treatment of

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419 the patient and organisations for which the patient has given explicit consent for data transfer (e.g.,
420 laboratory staff).

421 **Trial status**

422 Recruitment for the study opened in Nov-2020 and recruitment is expected to last for 5 years.

423 **Ethics and dissemination**

424 The study will be performed in accordance with the recommendations guiding physicians in biomedical
425 research involving human subjects, adopted by the 18th World Medical Association General Assembly,
426 Helsinki, Finland and stated in the respective participating countries laws governing human research, and
427 Good Clinical Practice. The protocol was initially approved on 18-Feb-2020 by West Midlands - Edgbaston
428 Research Ethics Committee; the current protocol (v3.0) was approved on 15-Jun-2022.

429 A meeting will be held after the end of the study to allow discussion of the main results among the
430 collaborators prior to publication. The results of this study will be disseminated through national and
431 international presentations and peer-reviewed publications.

432 Manuscripts will be prepared by the SMG and authorship will be determined by mutual agreement.

433 **Discussion**

434 **Justification for patient population**

435 The main aim of the TJBm study is to test the hypothesis that comprehensive genomic and epigenomic
436 profiling of gliomas is feasible in a timely manner in the UK, and that the results improve stratification of
437 patients for next generation (targeted) therapies, ultimately improving outcomes and QoL.

438 Gliomas occur at all ages and their specific subtype is difficult to predict preoperatively. Therefore, the
439 patient population eligible for the TJBm study is broad. It includes any patient who on preoperative
440 assessment is suspected to have a diffuse glioma, or where a diffuse glioma remains a credible differential
441 diagnosis, as established by the multidisciplinary team at the recruiting site.

442 Recruitment is also open to patients with diffuse or atypical gliomas who had a biopsy before the launch
443 of the TJBm study. This approach ensures that:

- 444 1. Patients with slow-growing diffuse gliomas that evolve over many years (oligodendrogliomas) may
445 benefit from one or more of the clinical trials developed as part of the TJBm study and sample
446 collection at tumour progression.
- 447 2. Patients who potentially benefit most from comprehensive molecular diagnostics are not missed,
448 which often are those with rare or atypical variants of glioma based on current diagnostics (34).

449 The infrastructure for children with brain tumours in the UK is different to that of adults with epigenomic
450 classification regularly used and with WGS shortly to be made available for all children with cancer. Thus,
451 the challenges and opportunities are different for paediatric patients. Nevertheless, it is intended that
452 children will be included within the TJBm study wherever appropriate. The recruitment of children and
453 adolescents into the TJBm study will be coordinated with the UK's paediatric oncology expert group(s).

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454 **Justification for methodology**

455 Neuroimaging with MRI plays a central role in the initial diagnosis and treatment stratification, surgical and
456 radiotherapy planning and assessment of disease response and progression in glioma.

457 Potential participants will have undergone MRI as part of a diagnostic work-up and an intracranial mass
458 identified. As per current clinical practice, expert neuroradiological review will indicate glioma as the likely
459 diagnosis, and a plan for treatment will be made by the relevant regional MDT meeting. Those with
460 suspected glioma on MRI who are to undergo surgery and are otherwise eligible for the TJBM study will be
461 approached. A proportion of these lesions that are subsequently diagnosed as types of brain tumours other
462 than glioma will inevitably be included. They will not be included in the main analysis; however, data from
463 these will be stored for additional research into those less common tumours which can be challenging to
464 diagnose from imaging alone.

465 At the time of surgery, neuro-navigation will be used to capture the location of each biopsy taken for
466 diagnosis and further molecular characterisation within the TJBM study. This will aid with subsequent
467 analysis of tumour molecular markers and heterogeneity in the context of radio-genomics – a recent
468 development in cancer imaging for assessment of disease in the personalised medicine era employing
469 machine learning and artificial intelligence approaches (32).

470 Early post-operative imaging for suspected HGG, including pre- and post-contrast T1-weighted MRI, is
471 currently recommended within 72 hours of surgery to minimise the presence of non-neoplastic
472 enhancement. This imaging will be captured to permit eventual assessment of extent of resection, or the
473 volume of residual enhancing disease, important prognostic factors for glioma. Subsequent to this, any
474 additional imaging for radiotherapy planning, including computerised tomography (CT), will be captured.
475 Under the most recent response assessment in neuro-oncology (34) recommendations for HGG from 2017,
476 this is recommended as the baseline for assessing treatment response (32).

477 All imaging will receive primary radiological reports at the local site as per current standard clinical practice.
478 To deliver the imaging outcome requirements for clinical trials, centralised RANO reads will be delivered
479 by a core group of UK Consultant neuro-radiologists with a subspecialty interest in neuro-oncology imaging
480 from TJBM study sites. Radiotherapy planning data in the form of dose distribution maps and associated
481 data will be integrated into the imaging database to permit subsequent analysis of spatiotemporal
482 response patterns of different glioma-treatment combinations in light of received radiation dose.

483 Local radiological reporting will inform clinical decision making for individual patients. Central image
484 analysis will provide resilient standardised assessment to meet internationally-accepted standards which
485 are suitable for peer-reviewed publication and are accepted by major regulatory approval bodies. All
486 relevant pre-operative and subsequent imaging will be identified for pseudonymisation and uploaded to
487 the BRAIN MATRIX Imaging Platform in Edinburgh. This will be achieved through a dedicated online secure
488 portal, with alternative secure online and physical transmission pathways available for redundancy. The
489 accrued imaging data will form a core resource that will be leveraged for future imaging and clinical
490 radiological research. The platform can also provide the basis for additional imaging studies within non-
491 standard of care imaging and advanced techniques, which would be separately funded and detailed in their
492 respective project documentation.

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493 **Justification for tissue collection**

494 Historical approaches to brain tumour tissue collection in formaldehyde and paraffin are not currently fully
495 compatible with modern genomic technologies, which require frozen tissue. This is why the collection of
496 fresh frozen (FF) material is essential for the TJBM study. Pairing with non-neoplastic, so-called germline
497 DNA, is also essential for confident calling of somatic variants in the tumour. Germline DNA analysis will
498 also provide novel data on genetic risk for glioma predisposition.

499 Blood plasma, where possible, will be collected to facilitate future analysis of cftDNA. This technology is
500 still in its infancy; however, it is clear that non-invasive, real-time monitoring of tumour evolution will
501 become feasible in the next 5-10 years (35). Similarly, where available for the patient, CSF will be submitted.

502 Post-mortem tissue banking via the CRUK PEACE and MRC Brain BioLink projects will allow us to study the
503 glioma-brain interface, extent of spatial tumour heterogeneity, genomic signature of the treatment
504 resistant tumour clones, and effect of treatments on normal brain. Systematic post-mortem brain banking
505 for research into adult gliomas does not currently exist in the UK.

506 **Justification for molecular diagnostics**

507 All TJBM study baseline diagnoses will follow the new WHO classification of tumours of the CNS from 2021
508 to achieve an integrated histological-molecular diagnosis for diffuse gliomas (10). This is achieved with a
509 combination of immunohistochemical surrogate markers and – in most instances – targeted or panel
510 sequencing for relevant hotspot mutations, or cytogenetics (7). Only in exceptional circumstances unbiased
511 ‘omics’ approaches are used, such as the epigenomic ‘Heidelberg Classifier’ (34). Further, any diagnostic
512 approach may differ between centres in the UK, making analyses of cohorts pooled from different sites
513 difficult.

514 The new WHO 2021 classification represents a consensus opinion based on new insights into the molecular
515 definition of brain tumours from cIMPACT-NOW. cIMPACT-NOW updates are not intended to supplant the
516 existing WHO classification, but to provide possible guidelines for practicing diagnosticians and future WHO
517 classification updates. It is clear from the first iterations of cIMPACT-NOW that any progress is driven by
518 next generation (‘omics’) molecular analysis, not by standard or targeted analyses. This insight underpins
519 the selection of molecular analytical tools for the TJBM platform, namely, combined paired (blood-tumour)
520 WGS DNA analysis integrated with the epigenomic ‘Heidelberg Classifier’ (34). To achieve this, the TJBM
521 study will build on the experience and UK infrastructure of the 100,000 genomes project led by GEL, which
522 introduced WGS pathways into clinical practice. Early results from WGS in non-brain cancer patients
523 suggest that virtually all patients could be mapped to existing or potential targeted therapies (36).
524 Prospective large-scale paired WGS sequencing studies in diffuse glioma patients have not been done;
525 however, experience from other brain tumours such as medulloblastoma, suggest that analysis of WGS
526 data will provide new insights into glioma subtype diversity, including alterations in specific non-coding
527 regulatory elements not evident from non-WGS genomic approaches (37). WGS data will capture all
528 currently known relevant variants and uncover novel variants relevant for a better understanding of
529 tumour evolution and response to treatment. WGS and epigenomic analyses are highly complementary
530 genomic approaches (37): WGS will establish all potentially actionable mutations and epigenomic
531 classification will establish an unbiased score for the precise classification of the glioma (34). Neither can
532 be achieved with conventional targeted sequencing approaches. Importantly, the epigenomic classification
533 by novel DNA methylation-based ‘Heidelberg Classifier’ has been shown to fundamentally alter clinical
534 diagnoses and histological grades in >10% of biopsies, leading to changes in therapy (34). Moreover, the
535 epigenomic array technology provides genomic copy number variant data, which in theory can also be

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536 inferred from WGS data. However, pipelines for this type of analysis from WGS data are just evolving and
537 it is predicted that comparative analysis of WGS and Illumina's EPIC BeadChip data will be bioinformatically
538 highly valuable. Finally, WGS and the EPIC array raw data will form a unique source for researchers who
539 will be able to access this data together with all clinical, imaging and histological data. Creating a relatively
540 future-proof, quality-controlled research infrastructure is one of the main aims of the TJBM study, in
541 addition to establishing feasibility of timely genomic diagnosis in the NHS setting.

542 the TJBM study is more than paired tumour/blood WGS and EPIC array analysis. As the former is being
543 rolled out in the NHS in England, the BRAIN MATRIX molecular neuropathology team will work with GEL
544 and other stakeholders (including industry) to explore the next-generation of tissue analytics (such as long-
545 read sequencing and mass spectrometry). This will result in a unique, prospectively acquired dataset that
546 will enable researchers to integrate data analysis across modalities and with outcomes and treatment
547 response.

548 **Justification for patient outcome and quality of life**

549 Clinical trials require prospective collection of clinical data to Good Clinical Practice (GCP) standards. This
550 platform will develop the infrastructure for the collection of this, enabling streamlined patient recruitment
551 into clinical trials. Evaluation of treatments and associated complications across patients will give an
552 accurate measure of adverse events associated with current standard of care treatment in practice in the
553 UK.

554 Maximising QoL for patients with diffuse glioma is important particularly given its poor prognosis;
555 therefore, standardised measures of QoL will be collected. In adults these have been selected for their
556 standardisation and ease of use and have been reviewed with input from Patient Public Involvement (PPI)
557 representatives. It is intended that in the future integration with The Brain Tumour Charity's BRIAN project
558 (REC Reference: 18/SC/0283) (19) will allow further understanding of patient reported outcome measures.

559

560 **Contributors**

561 CW (Chief Investigator and first author): conception and design of the study, drafting and review of paper.

562 JS: trial management team leader, study design, drafting and review of paper.

563 AP: Study Biostatistician, study design, drafting and review of paper.

564 RM: senior trial coordinator, review of paper.

565 VW: principal investigator (Birmingham), review of paper.

566 UP: neuropathologist (Birmingham), study design, review of paper.

567 HB: patient and public representative, study design, review of paper.

568 JA: study design, review of paper.

569 RS: design of the study, review of paper.

570 GT: conception and design of the study, review of paper.

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571 AM: conception and design of the study, review of paper.

572 OA: conception and design of the study, review of paper.

573 LB: Lead Biostatistician, design of study, drafting and review of paper.

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580 Clinical Trials Fellowship.

581 This study was supported by Experimental Cancer Medicine Centres (ECMC) funding (Ref. 25127) and by
582 the ECMC Network.

583 **Role of funders and sponsor**

584 Neither the sponsor nor funders had any role in study design, data collection, data analysis, data
585 interpretation or writing of the report. The corresponding author had full access to all the data in the study
586 and had final responsibility for the decision to submit for publication.

587 **Competing interests**

588 All other authors declare no competing interests.

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591 instrumental in making sure the patients' voice has been heard and incorporated into this study protocol.
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593 Stubbs, Richard Fox, Dr Sarah Bowden, Prof. Christina Yap, Dr Siân Lax and Dr Louisa Jeffery, and Hannah
594 Brooks at the University of Oxford for contributions to the protocol and paper.

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677

678 **Figure Legends**

679 **Figure 1: Overview of the Tessa Jowell BRAIN MATRIX Programme**

680 The Tessa Jowell BRAIN MATRIX Platform (TJBM) study will collect and integrate clinical, pathological,
681 advanced molecular, imaging, quality of life, treatment and outcome data. The platform may provide data
682 directly or support identification of eligible patients to clinical trials, within and outside the TJBM study
683 programme. If eligible, patients may be enrolled in multiple add-on studies. Through consent and with
684 strong governance processes, anonymised or pseudonymised data may be shared with other relevant
685 organisations or studies within and outside the programme.

686

687 **Figure 2: The Tessa Jowell BRAIN MATRIX Platform study schema**

688 The study schema for the Tessa Jowell BRAIN MATRIX Platform study.

689

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690 **Figure 3: The Tessa Jowell BRAIN MATRIX Platform study sample and data flow** 691 **pathways**

692 The sample and data flow pathways within the Tessa Jowell BRAIN MATRIX Platform (TJBM) study.

693 *TJBM sites in England are encouraged to route all samples through their local NHS GMS GLH, however, if
694 this pathway is not yet activated or GEL consent cannot be obtained, the TJBM Study Office can facilitate
695 the processing of samples through an alternative NHS GMS GLH or via the GEL Research pathway.

696 GEL, Genomics England; GLH, Genomic Laboratory Hub; GMS, Genomic Medicine Service; GTAB, Genomics
697 Tumour Advisory Board; NHS, National Health Service; WGS, Whole Genome Sequencing.

698

699 **Additional Files**

700 **Supplementary Appendix 1: Tessa Jowell BRAIN MATRIX Platform Study** 701 **Investigators & Committee Membership**

702 Principal Investigators, Study Management Group (SMG), Executive Oversight Committee (EOC) and
703 Scientific Advisory Board (SAB).

704

705 **Supplementary Appendix 2: The Tessa Jowell BRAIN MATRIX Platform study** 706 **SPIRIT Checklist**

707 A completed Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) checklist for the
708 Tessa Jowell BRAIN MATRIX Platform study protocol.

709

710 **Supplementary Appendix 3: The Tessa Jowell BRAIN MATRIX Platform study** 711 **World Health Organization Trial Registration Data Set**

712 The World Health Organization (WHO) trial registration data set for the Tessa Jowell BRAIN MATRIX
713 Platform study.

714

715 **Supplementary Appendix 4: The Tessa Jowell BRAIN MATRIX Platform study** 716 **informed consent form**

717 The informed consent form for the Tessa Jowell BRAIN MATRIX Platform study.

718

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719 **Supplementary Appendix 5: The Tessa Jowell BRAIN MATRIX Platform study**
720 **lay summary and patient information sheet**

721 The lay summary and patient information sheet for the Tessa Jowell BRAIN MATRIX Platform study.

722

723 **Supplementary Appendix 6: The Tessa Jowell BRAIN MATRIX Platform study**
724 **schedule of events**

725 Patient schedule of events for the Tessa Jowell BRAIN MATRIX Platform study.

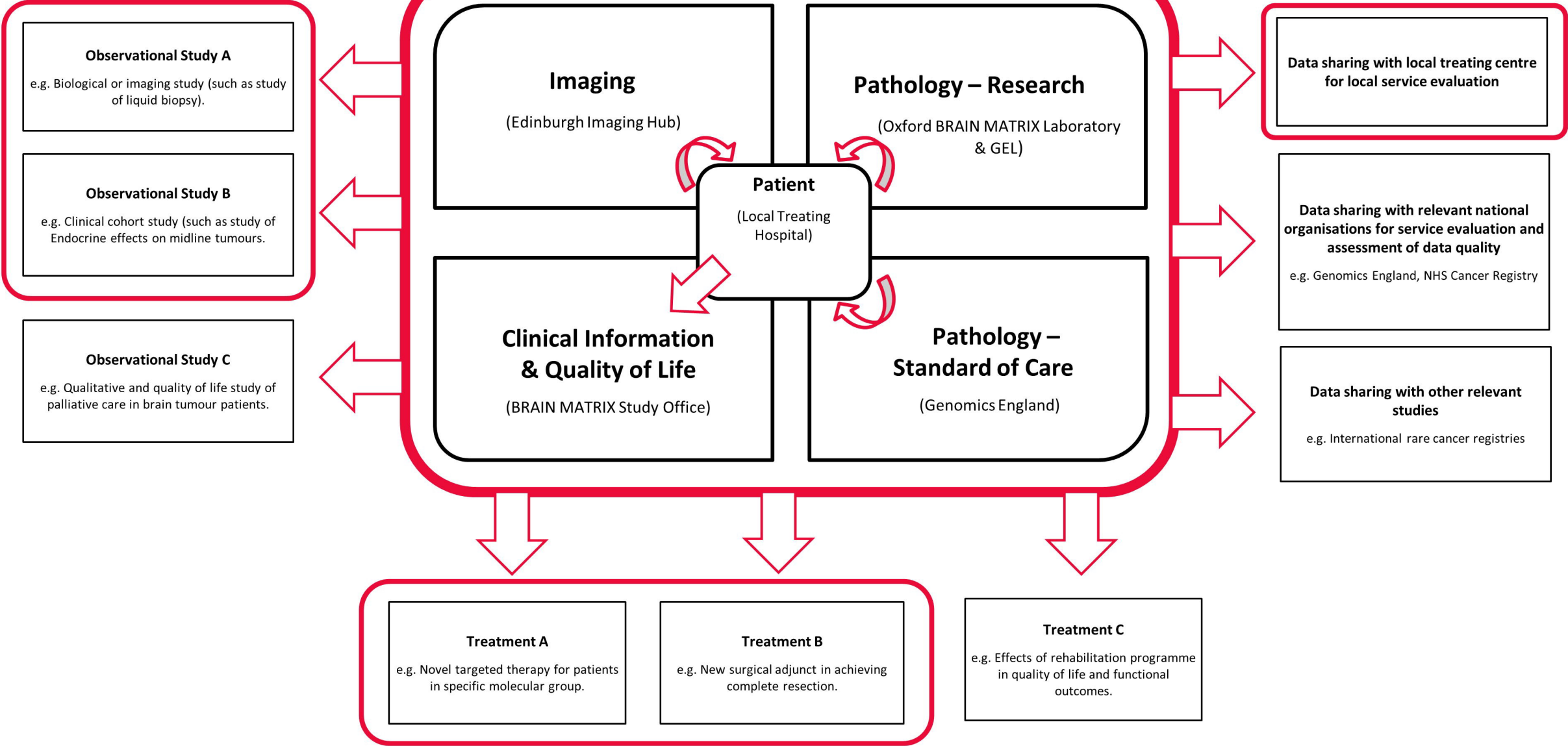
726

727 **Supplementary Appendix 7: Definition of adverse events**

728 Definitions of adverse events used for the Tessa Jowell BRAIN MATRIX Platform study.

729

TJBM PLATFORM STUDY



Newly diagnosed patient with suspected WHO grade 2-4 glioma and suitable for a diagnostic or therapeutic surgical procedure resulting in tumour sample matched to a blood sample

(Stereotactic biopsy, open biopsy, sub-total resection or gross total resection)

Patient with progression with known WHO Grade 2-4 glioma

(Those with available frozen tumour will be prioritised)

Study Registration with the BRAIN MATRIX Study Office

All cases and non-NHS pathway:

Tissue and blood sample sent to the Oxford BRAIN MATRIX Laboratory for biobanking, biofluid analysis and complementary multiomics

NHS GMS pathway:

Tissue and blood sample sent via GLH for WGS and EPIC methylation analysis

Imaging sent to the Edinburgh Imaging Hub

Follow up information collected for up to 5 years

Molecular/Genomic Tumour Board discussion and feedback of results

England

Blood/Tumour
DNA TJBM
study entry

All other fresh/frozen
tissues and samples from
non-NHS WGS episodes

NHS GMS GLH

Oxford BRAIN MATRIX
Laboratory Hub

NHS England
Plating Hub

Illumina / GEL Sequencing Centre (Cambridge)

Oxford BRAIN
MATRIX Laboratory

- Biobanking
- Novel omics
- cfT-DNA
- Data integration
and visualization
- Virtual GTAB

GEL Research
Environment
and/or
Local GMS GTAB

Devolved Nations*

Blood/Tumour DNA
TJBM study entry and any other fresh/frozen
TJBM samples

Oxford BRAIN MATRIX
Laboratory Hub

GEL Research Cohort
Plating Hub or
NHS GLH Plating Hub