BrainApp

Feasibility, acceptability and relationship to standard measures of near-patient sensing through a mobile app and machine learning - an observational non-randomised phase II trial in patients with primary brain tumours

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Protocol authorised by:

Name & Role	Date	Signature
Dr. Matthew Williams		
Dr. N. Aizaan Anwar		

Study Management Group

Chief Investigator: Dr Matthew Williams

Co-investigator: Dr. N. Aizaan Anwar

Statistician: N/A

Study Management: Imperial College Healthcare NHS Trust

Clinical Queries

Clinical queries should be directed to Dr Matthew Williams

Sponsor

Imperial College Healthcare NHS Trust is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Research Governance and Integrity Team
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG
Tel: **0207 594 9459/ 0207 594 1862**
http://www3.imperial.ac.uk/clinicalresearchgovernanceoffice

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This protocol describes **BrainApp: Feasibility, acceptability, and relationship to standard measures of near-patient sensing through a mobile app and machine learning - an observational non-randomised phase II trial in patients with primary brain tumours** and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Contents

List of abbreviations and definitions

ACE-27	Adult Comorbidity Evaluation 27
AE	Adverse event
AI	Artificial Intelligence
BT	Brain tumour
BTC	The Brain Tumour Charity
eCRF	Electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
HRA	Health Research Authority
ICHT	Imperial College Healthcare NHS Trust
IEP	Image Exchange Portal
MDT	Multidisciplinary team meeting
MHRA	Medicines & Healthcare products Regulatory Agency
ML	Machine Learning
NIHR	National Institute of Health Research
NCRN	NIHR Clinical Research Network
PIS	Patient Information Sheet
PPI	Patient and Public Involvement
QOL	Quality of life

Keywords: Mobile application, brain tumours, speech, balance, coordination, visual memory and quality-of-life

Study Summary

Title	BrainApp - Feasibility, acceptability and relationship to standard measures of near-patient sensing through a mobile app and machine learning - an observational non-randomised phase II trial in patients with primary brain tumours
Design	Observational non-randomised phase II trial
Aim & Objectives	Aim: To assess the feasibility, acceptability, and performance of a mobile app in collecting data on quality of life (QOL), physical activity and sleep, for predicting disease progression in brain tumour patients. Objectives: 1. To generate a prospectively collected dataset of patient measures obtained through mobile devices in brain tumour patients and healthy volunteers. 2. To assess compliance and performance of micro-challenges (hand coordination, visual memory, speech and facial features) in study participants using a mobile application. 3. To assess differences and systematic variation in micro-challenge performance between healthy volunteers and brain tumour patients. 4. To assess factors associated with micro-challenge performance in brain tumour patients, the relationship between micro-challenges and standard measures of QOL and disease progression. 5. To assess the diagnostic performance of different machine learning models in detecting brain tumour progression.
Outcome measures	Primary: Diagnostic performance of a machine learning model, measured as accuracy, recall, precision and F1 score. Secondary: 1. Compliance in micro-challenge use measured as one completed entry in the BRIAN app per month per subject. 2. Relationship between micro-challenge scores and participants' clinical progression and treatment. 3. QOL scores from the EORTC QLQ-C30 and BN20 questionnaires.
Population	1. Adults with a medically confirmed primary brain tumour diagnosis 2. Healthy adult volunteers
Eligibility	1. Age 16 and above 2. Fluent English speakers 3. Willing and able to undertake study-specific measures 4. Able to provide either electronic or written consent 5. Formally diagnosed with a primary brain tumour (either based on histology or assessment of imaging at a neuro-oncology MDT) or healthy volunteers 6. Brain tumour patients with a performance status of 0, 1, or 2.
Study duration	4 years

Lay summary

Brain tumours (BTs) are the leading cause of death in adults under 40. Although rare compared to other tumours, they can cause great disability and financial burden to both patient and caregiver. Even with specialist treatment, BTs usually progress, and many patients will not survive more than 2 years. Even in those patients who are well enough for treatment, at some point the tumour will often grow, causing new symptoms and requiring further treatment. Detecting this growth is currently done through scans (CT and MRI). However, these scans are time-consuming, expensive, and may not always give clear answers.

Many patients in whom the tumour grows will develop new symptoms, such as weakness down one side, speech, thinking or language problems. Computer-based analyses of speech, motion detection and visual features have been shown to differentiate between healthy individuals and those with other brain diseases (e.g. dementia). The increased use of "smartphones" and electronic tablets means that most adults now carry a device that can measure data on speech, movement, and balance; captured via "apps" which people download onto their device. Our research team at Imperial College London is already undertaking a study, called Brain Wear, to investigate the feasibility of wearable devices in assessing the level of physical activity in BT patients. Inspired by Brain Wear, we have designed BrainApp, to explore the potential of mobile apps in monitoring physical features and quality of life (QOL) in BT patients. Although there are hundreds of health-related apps in the market today, there is limited evidence for their effectiveness and very few of them focus on BTs. With this in mind, we are collaborating with The Brain Tumour Charity (BTC) which has designed and released a free app ("BRIAN") that allows users to enter information on their background diagnosis, treatment and QOL, as well as perform mini-games (Challenges) that test co-ordination, memory, changes in facial features and speech.

This study will use the data collected in BRIAN, and assess how well patients and healthy volunteers are able to use the app, and whether the data collected through the app correlates with traditional measures of treatment and disease progression. We are particularly interested in whether changes in the measures collected in BRIAN pre-date conventional measures of disease progression, measured using scans. Ultimately, this may enable the development of a tool that allows us to detect earlier signs of disease progression, and so offer earlier treatment and preservation of QOL; and hence the best course of action. Such a tool would also be non-invasive, cheap, quick, and able to be conducted at home.

1 Introduction

1.1 Background

Brain tumours (BTs) are abnormal growths in the brain which may cause a wide range of complications (including speech disturbances, headaches, sensory disturbances, seizures and death) depending on anatomical location and pathology [1]. BTs are the leading cause of cancer death in the under 40s[2] and has the highest Average Years of Life Lost compared to other tumours[3]. More than 90% of tumours in the central nervous system arise in the brain[4]. These tumours may arise from the brain tissue itself or be disseminated from other organs. They can either be malignant or benign[4]. Although relatively rare, BTs can cause significant disability and economic burden, with an incidence projected to rise with the aging global population[4–6]. BTs are treated with a combination of neurosurgery, radiotherapy and chemotherapy; based on multiple factors including symptoms, histological type, patient preference and functional ability[4,6,7]. Even with treatment, disease progression rates remain high, especially in malignant tumours[8,9]. This is compounded by the challenge in diagnosing disease progression, as the standard diagnostic tool which is gadolinium-enhanced Magnetic Resonance Imaging (MRI) cannot accurately discriminate between true tumour progression and side effects of chemo- and radiotherapy[7,8,10–12]. The lack of a more accurate method in detecting BT progression necessitates a diagnostic tool that is both effective and scalable.

1.2 Rationale

There is increasing ubiquity of healthcare-related mobile apps in the market for patient management and support[13–16]. Some of these apps are able to provide real-time assessments of external lesions[17], patient mood[18], physical symptoms[19], QOL[20], abnormal movements[21] and speech[22]. In addition, patients are also able to store their health records in these apps for sharing with different members of their healthcare team[14]. The multimodality of smartphone functions has enabled both objective and subjective measures of patients' experience to be evaluated for self-monitoring and as an aid to healthcare professionals. However, despite these positive developments, there is insufficient evidence on the effectiveness and safety of cancer-focused mobile apps (especially in BTs) and inadequate healthcare provider involvement[13,14,23]. This creates an opportunity for us to explore the potential of a mobile app that can obtain subjective and objective measures in BT patients' daily functioning as well as relate them to their disease status. Through built-in motion sensors, there is potential in detecting subtle changes to patients' limb coordination[24]. Patients with difficulty in navigating the app due to sensorimotor or cognitive difficulties may benefit from passive monitoring of their physical activity through motion detection[25]. Mobile applications can also be used to detect changes in facial features of patients with facial muscle weakness[26]. There is also the possibility of assessing patients' reaction times through specialised softwares[27,28].
Another modality that can be used in mobile-device-assisted monitoring is speech. As an acoustic signal for language transmission, speech provides a window into an individual's identity, physiology, emotion and cognition[29–33]. It is a potential tool that can be explored in prognosticating BTs, as its impairment has been noted to be one of the earliest signs of disease, regardless of anatomical location[34–36]. Speech production begins at the cognitive level and ends in production of air pressure[37–40]. Language is thus encoded in an analogue signal. Both this signal and its linguistic content can be analysed[40]. Currently, formal assessments of speech are labour-intensive, subject to inter-rater reliability, less specific to BTs and require face-to-face contact with trained assessors[33,35,36,41–44]. However, the advent of computerised speech analysis i.e. Natural Language Processing (NLP) enables automation of speech analysis, remote test administration and greater reliability[38,45,46]. There are no published studies on automated speech in BTs, however, there is clear evidence for the use of automated speech analysis in other diseases of progressive cerebral dysfunction[33,47,56–58,48–55]. The potential for remote monitoring of speech has also begun to be explored, where a study by Konig et al showed that voice recordings through a mobile application was able to classify dementia patients and healthy participants with an accuracy of 92%[22].

To the best of our knowledge, this study is projected to generate the first multimodal dataset of BT patients and potentially the largest pathological speech database in the world. Through this dataset, we will be able to link other forms of data on patients and tumours in developing machine learning approaches to multimodal data analysis. In addition, we will be able to provide data on feasibility, acceptability, and performance of near-patient monitoring using a mobile app in BT patients. It will enable future development of a decision-support tool that is near-patient, non-invasive, consistent, and scalable.

1.3 The BRIAN App

BRIAN (the Brain Tumour Information and Analysis Network) is a mobile application that allows individuals to anonymously record their experience living with a BT and share this information to both researchers and doctors[59]. BRIAN has been developed by BTC to help individuals cope with a BT. It allows participants to record their entire BT experience in one place - from symptoms, treatments, side effects, appointments, and QOL. In addition, BRIAN can link to other types of data such as physical activity and sleep, both from a phone and wearable device linked to the phone (e.g. Fitbit and Apple Watch). Users of BRIAN can choose with whom to share their data, and data in BRIAN is secure – more information is available here: https://askbrian.org.uk/your-data.

BRIAN has been developed to contain a range of options for data recording and collection, including the ability to schedule appointments, complete QOL questionnaires, record medication, check access to financial benefits and find clinical trials. In addition, there are also four "micro-challenges" – small "games" that users can play on the app which takes up to 5 minutes to complete in total. These include a "stability" game, where users must balance a circle on the screen; a game of "snap" involving matching abstract, coloured shapes; a reading challenge (reading a paragraph of text aloud and recording it); and uploading a photograph of the user's face (a "selfie"). Users can also opt to link their physical fitness data (obtained either from the mobile device itself or wearable devices) on to BRIAN.

1.4 Patient and Public Involvement

The development of the BrainApp study has had a long history of patient and public involvement (PPI). It is a development of our existing BrainWear study (ISRCTN: 34351424), which was initially inspired by a patient asking about whether we could use their Fitbit data. Patients and carers will be involved throughout the lifecycle of the research. We have had a PPI group meeting from our local Neuro-oncology PPI group regarding consenting methods, types of tasks participants need to do, how much and how often. Patients and their carers preferred electronic methods of giving information and consenting. They are happy to undertake the tasks at the frequency and volume proposed in the protocol. Their feedback informed the design of the tasks participants need to do for this study.

We will hold regular focus groups remotely to obtain feedback from participants regarding the usability of BRIAN, and patients will be part of the trial management group. We will also involve them in designing the analysis (i.e. key questions to ask) and in helping us both design and deliver the dissemination of the findings.

2 Study aim & objectives

2.1 Aim

To assess the feasibility, acceptability, and performance of a mobile app in collecting data on QOL, activity and sleep, for predicting disease progression in BT patients.

2.2 Objectives

1. To generate a prospectively collected dataset of patient measures obtained through mobile devices in BT patients and healthy volunteers.
2. To assess compliance and performance of micro-challenges (hand coordination, visual memory, speech and facial features) in study participants using a mobile application.
3. To assess differences and systematic variation in micro-challenge performance between healthy volunteers and BT patients.
4. To assess factors associated with micro-challenge performance in BT patients, the relationship between micro-challenges and standard measures of QOL and disease progression.
5. To assess the diagnostic performance of different machine learning models in detecting BT progression.

3 Study design and methodology

3.1 Study design

This is a phase II non-randomised observational study recruiting BT patients and healthy volunteers. It is aimed at assessing the performance of a machine learning classifier developed from a multimodal dataset in predicting BT progression. We aim to recruit two parallel subject cohorts over two years. The first cohort (A) will consist of cancer centre patients, whilst the second cohort (B) will be healthy volunteers. The study will involve the use of a mobile application developed by BTC, called BRIAN, as the primary assessment tool; along with electronic case report forms (eCRFs) and brain scan images.

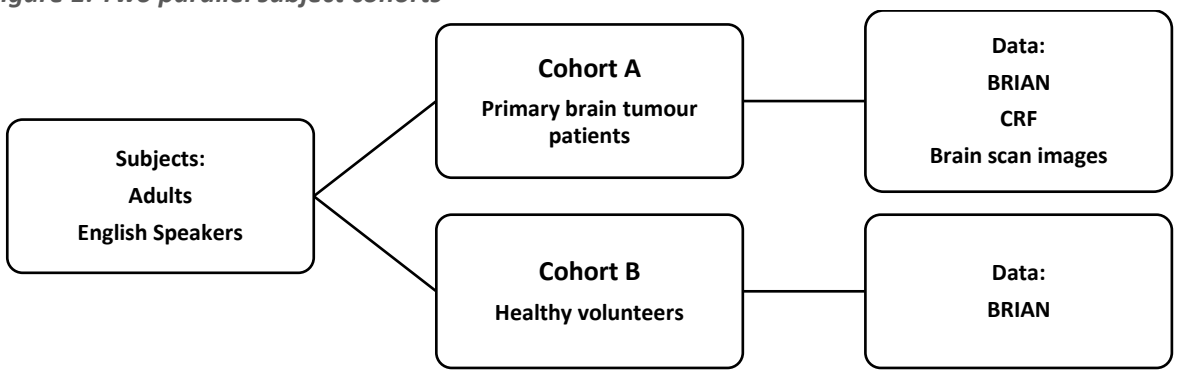
3.2 Sample size

It is not, in general, possible to calculate required sample sizes for machine learning tools. Larger samples sizes not only allow for better performance, they also allow for better generalisability of performance. Given that this trial runs alongside standard treatment, and there are 10000 adult patients diagnosed with a primary brain tumour in England every year, although only ~60% have active treatment. We expect that the trial will be most attractive to patients who are starting active treatment. Obviously, not all patients will want to take part in clinical research, but we think that a target of 10000 is feasible. We will recruit as many patients and healthy volunteers as possible, up to a maximum of 10000 subjects.

3.3 Participants

There will be two parallel cohorts of subjects (Fig 1): 1) Cohort A will consist of BT patients recruited via cancer centres and 2) Cohort B will consist of healthy volunteers. Data from Cohort A will be obtained via the BRIAN mobile application, eCRFs and brain scan images; whereas data from Cohort B will be obtained solely via BRIAN (Table 1).

Figure 1: Two parallel subject cohorts



3.4 Assessments

3.4.1 BRIAN APP

BRIAN is a mobile application developed by BTC that allows individuals to anonymously record their experience living with a BT and share this information with both researchers and doctors[59]. It is designed to help individuals cope with a BT and allows participants to record the entire BT experience in one place - from symptoms, treatments, side effects, appointments, and QOL. In addition, BRIAN can link to other types of data also captured by users' smartphones, such as physical activity and sleep, both from the phone and devices connected to the phone (e.g. Fitbit and Apple Watch). Users of BRIAN can choose with whom to share their data.

All subjects in this study will use BRIAN as the main assessment tool (Table 1). Patients may ask their caregiver or health professional to assist in entering information into the app. Participants in the trial will be asked to share their data with the trial team explicitly, and have the freedom to withdraw permission for data sharing at any time. Data storage in BRIAN is well secured – more information is available here: https://askbrian.org.uk/your-data

3.4.1.1 What do participants need to do using the BRIAN app?

1. **BRIAN Profile**: Record date of birth, sex, subject type (patient or healthy volunteer), country of residence and qualifications.

2. **Handedness**: Record whether left- or right-handed

3. **Medication:** Record medication name.

4. **Trial information** (Cohort A only): Record their clinical trial name, eCRF number, location, start date and end date.

5. **Tumour log** (Cohort A only): Record tumour type, grade, location, status, baseline radiology report and baseline histology report as well as date of diagnosis (estimated date if patient unable to recall exact date).

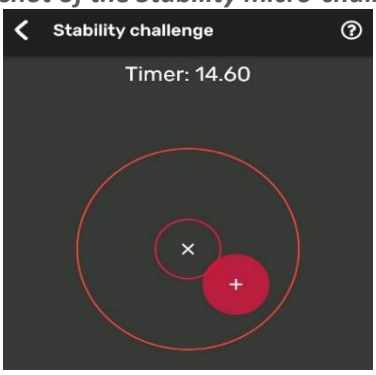
6. **Treatments & appointments log** (Cohort A only): Record appointment type, date, time, and radiology report (if applicable), as well as hospital/ clinic where they are being treated. This will allow us to relate any changes to assessments with clinical events and enable retrieval of histopathology and radiology reports from cancer centres.

7. **QOL assessment with EORTC QLQ-C30/BN20 combined questionnaire :** – Only Cohort A will be required to complete this questionnaire.

    a. EORTC QLQ-C30 covers five functioning scales (physical, social, role, cognitive, and emotional functioning), eight symptom scales (fatigue, nausea/vomiting, pain, dyspnoea, sleep disturbances, appetite loss, constipation, and diarrhoea), financial impact, and overall QOL, and the scores are linearly converted to range between 0 to 100. High scores in the functioning scale and global QOL indicate better function whilst a higher score in the symptom scale indicate higher symptom burden. See: https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-QLQ-C30-English.pdf.
    b. EORTC QLQ-BN20 questionnaire covers a further 11 scales to assess neurological deficits (visual disorder, motor dysfunction, communication deficit), future uncertainty, and disease- and treatment-related symptoms. Similar to the EORTC QLQ-C30, the raw scores are converted to a 0-100 scale and a higher score for this questionnaire represents a poorer QOL. See: https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-BN20-English.pdf.

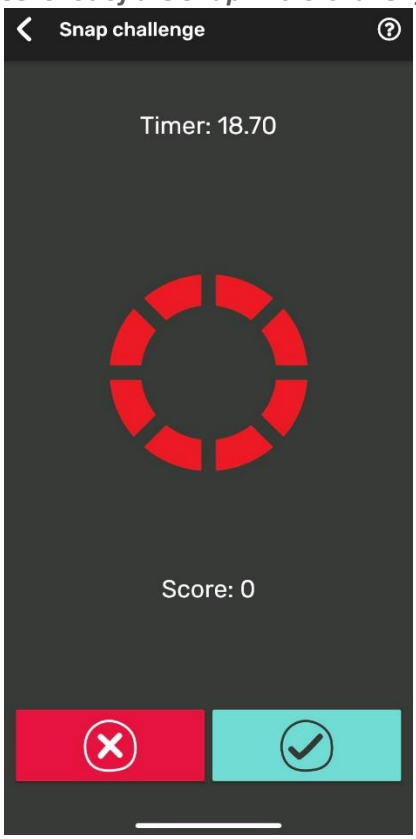
8. **Micro-Challenges:**
    a. Stability: Users will need to keep a circle in the middle of the screen for 20 seconds (Fig 2) by gently and gradually tilting their mobile device to maintain the same position. This will be used to assess users' visual and motor coordination.

Figure 2: Screenshot of the Stability micro-challenge on BRIAN.



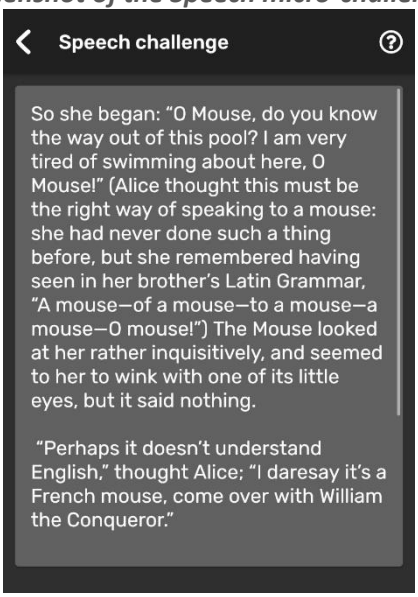
b. Snap: Review 20 pairs of images and decide whether they match or not (Fig 3). This will be used to assess users' visual memory.

Figure 3: Screenshot of the Snap micro-challenge on BRIAN



c. Speech: Read aloud a paragraph of text while being recorded by BRIAN (Fig 4). This will be used to assess any vocal and language changes over time.

Figure 4: Screenshot of the Speech micro-challenge on BRIAN



   d. Photo: Take a photograph of your face (a "selfie") and upload it. This will be used to assess for any facial feature changes.

9. **Fitness tracking**: Participants can opt to link either their wearable fitness trackers or smartphone fitness trackers with BRIAN. This allows us to assess how users' physical activity and sleep vary over time and with treatment, as both are commonly affected in Brain Tumour patients.

3.4.1.2 Utilising the BRIAN app – enrolment to end of study

1. **REGISTRATION**: This is done on the day of enrolment and when demographic and medical information changes. All subjects will be required to enter their BRIAN profile and medication. Cohort A will be required to complete their tumour log and trial information.

2. **INTERVAL**: Performed on a monthly basis at a minimum.
   a. **Micro-challenges** – Performed by all subjects.
   b. **QOL questionnaire** – Only Cohort A will be required to complete this questionnaire.

3. **AD HOC**: Performed by Cohort A only.
   a. **Treatments & appointments log:** To be entered when information becomes available.
   b. **Tumour log:** To be entered if tumour status changes.
   c. **Micro-challenges:** To be self-administered within five days before and after any treatments or appointments.
   d. **QOL questionnaire:** To be self-administered within five days before and after any treatments or appointments.

4. **CONTINUOUS**: All subjects can opt to link their fitness trackers with BRIAN on the day of enrolment.

3.4.2 Case report forms

ECRFs will be designed using REDCap (Research Electronic Data Capture), which is a data collection tool with a simple secure web-based interface designed for clinical researchers (Imperial College London is a registered partner with the REDCap consortium). MRI and histopathology reports, along with co-morbidities and details of treatment received will be obtained from REDCap eCRFs for Cohort A only. Participating cancer centres will

be instructed to return the eCRFs via REDCap at subject enrolment, then 6-months, 12-months, and 24-months post-enrolment.

1. **Baseline eCRFs**:
    a. Demographic information: Date of recruitment, sex and year of birth
    b. Co-Morbidities as per the validated Adult Comorbidity Evaluation 27 (ACE-27) instrument[60]
    c. Date of brain tumour diagnosis
    d. Tumour histology: Date of all histology reports and all histology reports up to and including the date of patient enrolment
    e. Tumour imaging: Date of all imaging reports and all imaging reports up to and including the date of patient enrolment
    f. Treatment: Date and schedule of treatment received up to and including the date of patient enrolment.

2. **6-month eCRFs**:
    a. Demographic information: Date of recruitment, sex and year of birth
    b. Tumour imaging: Date of all imaging reports and all imaging reports since enrolment
    c. Treatment: Date and schedule of treatment received since enrolment.

3. **12-month eCRFs**:
    a. Demographic information: Date of recruitment, sex and year of birth
    b. Tumour imaging: Date of all imaging reports and all imaging reports since the last eCRF submission.
    c. Treatment: Date and schedule of treatment received since the last eCRF submission.

4. **24-month** eCRFs**:**
    a. Demographic information: Date of recruitment, sex and year of birth
    b. Tumour imaging: Date of all imaging reports and all imaging reports since the last eCRF submission.
    c. Treatment: Date and schedule of treatment received since the last eCRF submission.

3.4.3 Imaging Transfer

For patients in Cohort A, we ask centres to complete eCRFs and transfer imaging at enrolment, then 6-months, 12-months and 24-months post-enrolment. This can be done in one of two ways:

a) Trusts can transfer them using the standard secure NHS Image Exchange Portal (IEP), and then we will anonymise and export to research store locally using a process that has already been approved by ICHT and Imperial College London in terms of Information Governance.

b) Trusts can anonymise and transfer electronically, using the secure NHS OneDrive. This ensures that Trusts can use their own approved process, and so satisfy their own Information Governance requirements.

3.5 Methodology

3.5.1 Recruitment

Cohort A

Patients who are suitable for enrolment into this study will be approached by the treating doctor, clinical nurse specialist or clinical research practitioner who are all part of the direct care team.

Cohort B

Subjects who are carers and family members can be introduced to the study through clinic. Others will be recruited from advertisements via leaflets, posters, BTC website, and social media.

3.5.2 Consent

Cohort A

Patients who appear to meet the inclusion criteria will be offered verbal information on the study by members of the clinical team. If interested, either an electronic or paper Patient Information Sheet (PIS) will be given to the patient. If the patient is happy to participate in the study, they will be asked to download BRIAN. The patient can view the same PIS again on BRIAN if they wish to do so. One of the study team members will document informed consent (either electronically on BRIAN, via postal consent or paper consent) and complete the baseline eCRF. Once the consent form has been signed electronically on BRIAN, the participant can view a static version of the form and download it on to their own device prior to submission. Following submission, a copy of the form will be saved securely in the online project repository.

During the discussion of the study with patients, they will be made aware that participation is voluntary and that if they chose not to participate, it will not affect their care and treatments including their relationship with members of the direct care team. The right of the participant to refuse to participate without giving reasons shall be respected. All participants are free to withdraw at any time from the study without giving reasons and without prejudicing further treatment. If a participant loses their capacity to consent whilst taking part in the study, we will retain any existing data collected, but will not collect any further data and the patient will be withdrawn from the study.

Cohort B

Healthy volunteers will download the BRIAN app and read the PIS. Once they are satisfied with the conditions of the study, they will sign an electronic consent form on BRIAN. Once the consent form has been signed electronically, the participant can view a static version of the form and download it on to their own device prior to submission. Following submission, a copy of the form will be saved securely in the online project repository.

3.5.3 Steps

Cohort A:

1. Subject recruitment.
2. Subject downloads BRIAN.
3. Subject given PIS to read, agrees to study and signs consent form either electronically on BRIAN, by post, via email or face-to-face.
4. Subject enrolment into trial.
5. Participating centres complete eCRFs at enrolment, then 6-months, 12-months and 24-months post-enrolment (see table 1).
6. Participating centres to transfer brain scan images at enrolment, then 6-months and 24-months post-enrolment (see table 1 and section 3.4.3).
7. Subject to complete registration data and opt to link their fitness tracker on BRIAN (see table 1).
8. Subject to perform micro-challenges and EORTC QOL questionnaire monthly at a minimum.
9. Subject to perform micro-challenges and complete QOL questionnaire within five days before and after any clinical encounter.
10. Subject to enter any changes to BRIAN profile and medication as they occur.
11. Subject to complete tumour log if tumour status changes.
12. Subject to complete treatment & appointment logs when information becomes available.

Cohort B:

1. Subject recruitment.
2. Subject downloads BRIAN and reads PIS for healthy volunteers.
3. Subject signs consent form electronically.
4. Subject to complete registration data and opt to link their fitness tracker on BRIAN (see table 1).
5. Subject to perform micro-challenges monthly at a minimum.
6. Subjects to enter any changes to profile and medication as they occur.

Participating Cancer Centres

1. After consent has been gained, the study team member will inform the patient to enter their unique eCRF ID number on BRIAN while the study team member enters the patient's BRIAN ID on the eCRF.
2. At enrolment, the baseline eCRF form will be completed and all of the patients' brain scan images will be transferred via IEP to ICHT.
3. At 6 months post-enrolment, the 6-month eCRF and all the patients' new brain scan images will be anonymised and transferred to ICHT.
4. At 12 months post-enrolment, the 12-month eCRF following the previous eCRF will be transferred to ICHT.
5. At 24-months post-enrolment, the 24-month eCRF and all the patients' brain scan images following the previous eCRF will be anonymised and transferred to ICHT.

3.6 Data collection

There will be three sources of data for this study (Table 1): BRIAN app, eCRFs and brain scan images. Subjects from both cohorts will use BRIAN. Only Cohort A will have data from eCRFs and brain scan images.

Table 1: Assessment data to be collected

Data	Sources	Cohort	BRIAN Assessment Type	Purpose	Comment
Age	BRIAN	A & B	Registration	Explanatory variable	
Sex	BRIAN	A & B	Registration	Explanatory variable	
Qualification	BRIAN	A & B	Registration	Explanatory variable	Highest level of education attained
Subject type (patient/ healthy volunteer)	BRIAN	A&B	Registration	Cohort subgroup	To be added to BRIAN
Handedness	BRIAN	A & B	Registration	Explanatory variable	To be added to BRIAN
Medication	BRIAN	A & B	Registration Ad hoc	Explanatory variable	
Physical activity	BRIAN	A & B	Continuous	Explanatory variable	Subject to link fitness tracker to BRIAN
Speech challenge	BRIAN	A & B	Interval Ad hoc	Main explanatory variable	

Stability challenge	BRIAN	A & B	Interval Ad hoc	Main explanatory variable	
Snap challenge	BRIAN	A & B	Interval Ad hoc	Main explanatory variable	
Photo challenge	BRIAN	A&B	Interval Ad hoc	Main explanatory variable	
Trial end date	BRIAN	A	Registration	Trial information	To be added to BRIAN
Tumour type	BRIAN	A	Registration Ad hoc	Explanatory variable	
Tumour grade	BRIAN	A	Registration Ad hoc	Explanatory variable	
Tumour location	BRIAN	A	Registration Ad hoc	Explanatory variable	
Tumour status	BRIAN	A	Registration Ad hoc	Explanatory variable	
Date of diagnosis (exact or estimated)	BRIAN	A	Registration Ad hoc	Explanatory variable	
QOL (EORTC QLQ-C30/ BN-20 Questionnaire)	BRIAN	A	Interval Ad hoc	Explanatory variable	
Treatments	BRIAN	A	Ad hoc	Explanatory variable	
Appointments	BRIAN	A	Ad hoc	Explanatory variable	
Dates of treatments and appointments	BRIAN	A	Ad hoc	Explanatory variable	
MRI Image	Brain scan images	A	N/A	To assess tumour progression (outcome variable)	Obtained via IEP or other secure means at baseline, 6-months and 24-months
Co-Morbidities as per ACE-27	eCRFs	A	N/A	Explanatory variable	eCRFs to be returned at enrolment, 6-months, 12-months and 24-months
MRI report	• BRIAN • Brain scan images • eCRFs	A	Registration Ad hoc	To assess tumour progression (outcome variable)	eCRFs to be returned at enrolment, 6-months, 12-months and 24-months

Histopathology report	• BRIAN • eCRFs	A	Registration Ad hoc	Explanatory variable	eCRFs to be returned at enrolment, 6-months, 12-months and 24-months
Treatment date and schedule of treatment	• BRIAN • eCRFs	A	Registration Ad hoc	Explanatory variable	eCRFs to be returned at enrolment, 6-months, 12-months and 24-months

3.7 Study outcome measures

3.7.1 Primary:

Diagnostic performance of a machine learning model, measured as accuracy, recall, precision and F1 score.

3.7.2 Secondary:

1. Compliance in micro-challenge use measured as one completed entry in the BRIAN app per month per subject.
2. Relationship between micro-challenge scores and participants' clinical progression and treatment.
3. QOL scores from the EORTC QLQ-C30 and BN20 questionnaires.

4 Participant entry

4.1 Healthy volunteer

4.1.1 Inclusion criteria

I. Age 16 and above
II. Fluent English speaker
III. Willing and able to undertake study-specific measures
IV. Able to provide either electronic or written consent

4.1.2 Exclusion criteria

I. Subjects lacking capacity to consent
II. Refusal to participate
III. Subject not in possession of personal mobile device compatible with the BRIAN app

4.2 Patient

4.2.1 Inclusion criteria

I. Age 16 and above
II. Fluent English speakers
III. Formally diagnosed with a primary BT (either based on histology or assessment of imaging at a neuro-oncology MDT)
IV. Performance status of 0, 1 or 2
V. Willing and able to undertake study-specific measures
VI. Able to provide either electronic or written consent

4.2.2 Exclusion criteria

I. Subjects lacking capacity to consent based on patient's doctor's opinion
II. Diagnosis of secondary brain tumour (i.e cancer that starts somewhere in the body and spreads to the brain)
III. Refusal to participate
IV. Subjects with performance status of 3 or more
V. Subject not in possession of personal mobile device compatible with the BRIAN app

4.2.3 Withdrawal criteria

Subjects will be free to withdraw from the study at any time point without it influencing their care. Patients will be withdrawn from the study when they reach PS 3 for more than 2 weeks.

5 Assessment and follow-up

Subjects will be followed-up for a maximum of two years. Patients and healthy volunteers will be followed from enrolment for a duration of two years, discontinuation of treatment, or death - whichever occurs first. All BRIAN assessments will be done remotely on subjects' own mobile devices as per section 3.5.3.

6 Adverse events

Any untoward medical occurrence in a patient or clinical study subject shall be considered as an adverse event. If a participant loses his or her capacity whilst taking part in the trial, we will retain previously collected data, but no further data will be collected. It is not anticipated that any adverse events will occur due to the nature of the study which consists of assessments and questionnaires via a mobile application which do not involve clinically-invasive procedures. However, any questions concerning adverse events reporting will be directed to the Chief Investigator.

7 Statistics and data analysis

This study will be NCRN-badged and will be supported by the local NCRN research nurses. Anonymised data donated to the BRIAN APP will be held in a secured database with BTC then transferred to and stored at Imperial College London securely. For data obtained from cancer centres, these will be anonymised within each recruiting centre where it will be stored securely. All data will be handled in accordance with data protection and information governance guidance. Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period. As computational techniques improve, there is the potential to develop novel techniques to improve our analysis of such data. We expect such data to become increasingly important over the next 5 - 10 years, and therefore having a validated linked dataset is important for technical developments and further research in monitoring multimodal data. We will seek explicit consent to store the enrolment log, consent form and coded data for 10 years following completion of the study. Patient identifiable data, if electronic will be kept on the secure ICHT Computing system, or if in paper format will be stored within the secure research office within the Trust. The data will initially be analysed with conventional statistical methods (e.g. descriptive statistics and repeated measures multilevel modelling) which will inform machine learning methods to be employed.

8 Regulatory issues

8.1 Ethics approval

The Chief Investigator has obtained approval from the xxx Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 Funding

This work has been funded via a PhD studentship by the United Kingdom Research and Innovation Centre for Doctoral Training in AI for Healthcare http://ai4health.io (Grant No. EP/S023283/1).

8.7 Audits

The study shall be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research.

8.8 Peer review

The study has been reviewed by two independent external reviewers arranged by Imperial College's Research Governance and Information Team.

The study design has also been reviewed by the Imperial College London Computational Oncology Lab members which consist of five clinical academics, three research officers, one PhD candidate in Artificial Intelligence and one Biomedical Master's student. The study has also been discussed with a professor of machine learning at Imperial College London.

We are also submitting it for review at the NCRI Brain Tumour Study group.

9 Study Management

The day-to-day management of the study will be co-ordinated through the research nurse team at Charing Cross hospital, supported by Dr Williams and an Honorary Clinical Research Fellow.

10 Publication policy

We will publish and disseminate the results at local, national, and international meetings, and in peer-reviewed journals. We expect the work here to result in significant, novel findings, and to act as the basis for significant further grant applications.

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