UNIVERSITY OF CAMBRIDGE

Cambridge University Hospitals NHS Foundation Trust

**Clinical Trial Protocol**

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| Study Title: | Social Cognition Assessment and Rehabilitation for Families living with Brain Tumour (SCARF-BT): a Feasibility Study |
| Protocol Number: | SCARF-2019 |
| Study Funder:<br>Funder Reference: | NIHR Research for Patient Benefit<br>NIHR200495 |
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Protocol Signatures:

I give my approval for the attached protocol entitled Social Cognition Assessment and Rehabilitation for Families living with Brain Tumour (SCARF-BT): a Feasibility Study dated 18/03/2021

**Chief Investigator**

Name: STEPHEN PRICE

Signature: _____

Date: _____

**Site Signatures**

I have read the attached protocol entitled Social Cognition Assessment and Rehabilitation for Families living with Brain Tumour (SCARF-BT): a Feasibility Study dated 18/03/2021 and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and the GCP Directive 2005/28/EC.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

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Date: _____

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## 2 Abbreviations

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| AE | Adverse event |
| BN20 | Brain tumour 20 questionnaire (with QLQ-30) |
| CogENT | The Cognition Evaluation for patients with Neurological Tumours |
| CQOLC | Caregiver Quality of Life Index-Cancer |
| CRF | Case report form |
| CTCAE | Common terminology criteria for adverse events |
| DANVA-2-AF | Diagnostic Assessment of Non-verbal Acccuracy-2, Adult Faces |
| EORTC QLQ-30 | European Organisation for Research and Treatment of Cancer - Quality of Life Scale |
| FIM | Functional independence measure |
| GCP | Good clinical practice |
| GP | General practitioner |
| HRA | Health Research Authority |
| IDEAL | Idea, Development, Exploration, Assessment, Long-term Follow-up, (Improving the Quality of Research in Surgery) |
| MDT | Multidisciplinary team meeting |
| NCI | National Cancer Institute |
| NHS | National Health Service |
| OCS-Bridge | Neuropsychology screening tool (details https://ocs-bridge.com/about) |
| PPI | Patient and public involvement |
| REC | Research Ethics Committee |
| RfPB | Research for patient benefit |
| SAE | Serious adverse event |
| SCARF-BT | Social Cognition Assessment and Rehabilitation for Families living with a Brain Tumour (SCARF-BT): a Feasibility Study |
| SIND | Assessing impact of surgically-induced deficits on patient functioning and quality of life |
| SMG | Study management group |
| TAS-20 | The Toronto Alexithymia Scale-20 |
| TASIT | The Awareness of Social Inference Test |
| TBI | Traumatic brain injury |
| WHO | World Health Organisation |

## 3 Study Synopsis

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|---|---|
| Title of clinical study | Social Cognition Assessment and Rehabilitation for Families living with Brain Tumour (SCARF-BT): a Feasibility Study |
| Sponsor name | Cambridge University Hospitals NHS Foundation Trust |
| Medical condition or disease under investigation | Newly diagnosed glioblastomas |
| Purpose of study | Explore the feasibility of screening for and then providing a rehabilitation protocol for emotional recognition. |
| Study Design | This is a two-stage feasibility study with a parallel qualitative study.<br>• STAGE 1: a cohort study<br>• STAGE 2: a placebo-controlled feasibility randomised controlled study<br>• Parallel qualitative study: using interviews and/or focus groups at three stages:<br>a. Before start of study (before Stage 1)<br>b. After Stage 1<br>c. After Stage 2 |
| Study objectives | This is a feasibility study and as such our objectives relate to feasibility.<br><br>*Stage 1: the cohort study*<br>The specific objectives for this stage of the study are:<br><br>1. To examine if patients are able to complete the intervention with the support of a psychologist (defined as completing all 9 sessions of training).<br>2. To study, document and understand the iterative changes of a new technique for delivering a rehabilitation intervention (FACES – computer based training programme) and provide a narrative account of these changes until a stable technique has been developed (as described for Stage 2a IDEAL interventions[18]).<br>3. To assess acceptability of intervention as part of the parallel qualitative study.<br>4. Feasibility of assessment completion, by recording established validated outcome assessments patients are able to complete.<br>5. Feasibility of quality of life completion by both patient and carer |

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| | *Stage 2: placebo-controlled feasibility randomised controlled trial*<br>The specific feasibility objectives for this stage are:<br><br>1. To explore if we are able to screen patients for deficits in emotional recognition using OCS-Bridge (https://ocs-bridge.com/about).<br>2. To assess acceptability of the intervention, based on patients meeting the eligibility criteria that give consent for the study. This will be explored further as part of the parallel qualitative study.<br>3. To assess the ability to complete the active FACES intervention and control intervention.<br>4. To assess the acceptability of a number of established, validated outcome assessments as part of the parallel qualitative study.<br>5. To assess the impact on patient reported quality of life.<br>6. To assess the impact on patient's families.<br>7. To compare the impact of the active FACES intervention with the control intervention on scores for selected assessments.<br><br>*Parallel Qualitative Study*<br>Using interviews and/or focus groups involving both patients and their carers. The objectives for this parallel study before Stage 1, following Stage 1 and following Stage 2are:<br><br>1. To explore the experiences and perspectives of people with tumour, and carers regarding their lived experience and the perceived importance of the proposed intervention.<br>2. To explore their experiences of the intervention including preferred/suitable intervention content and delivery formats, experience of randomisation and potential barriers and facilitators to intervention delivery.<br>3. Perceptions of outcome measures and whether they capture the issues of importance to people completing the intervention.<br>4. To explore the experiences and perspectives of health care professionals regarding their experiences of delivering the intervention, and |

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| | potential barriers and facilitators to further delivery of the intervention within routine clinical services. |
| Outcome Measures:<br>STAGE 1 | 1. Percentage of patients completing the intervention (defined as completing all 9 sessions)<br>2. Prospective recording of any changes to the administration, conduct and content of the rehabilitation intervention on a patient-by-patient basis.<br>3. The acceptability of the intervention will be explored through a parallel qualitative study<br>4. Percentage of patients completing the following validated outcome assessments.<br>a. Diagnostic Assessment of Non-verbal Accuracy-2, Adult Faces (DANVA2-AF);<br>b. Emotion Recognition and Social Inference: The Awareness of Social Inference Test (TASIT), (part 1, EET subtest);<br>c. The Toronto Alexithymia Scale-20 (TAS-20).<br>5. Percentage of patients and carers able to complete quality of life questionnaires. |
| Outcome Measures:<br>STAGE 2 | 1. Screening rate to identify potentially suitable patients.<br>2. Percentage of screened patients meeting the eligibility criteria that provide informed consent for the study.<br>3. Percentage of patients who have completed all sessions for the FACES intervention (active intervention) and General Cognition Control Intervention (control intervention).<br>4. For each of the following established validated outcome assessments we will measure completion rates pre- and post-intervention.<br>a. Diagnostic Assessment of Non-verbal Accuracy-2, Adult Faces (DANVA2-AF);<br>b. Emotion Recognition and Social Inference: The Awareness of Social Inference Test (TASIT), (part 1, EET subtest);<br>c. The Toronto Alexithymia Scale-20 (TAS-20).<br>Acceptability will be explored with our parallel qualitative study.<br>5. Patient reported quality of life (using the EORTC QLQ-30 with the BN20 brain tumour module[19]).<br>6. The impact of these problems on patient's families (using the Caregiver Quality of Life Index-Cancer - CQOLC).<br>7. Difference in scores pre and post intervention for the selected assessments for both the active |

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| | (FACES) intervention group and the control intervention group. |
| Outcome measures: PARALLELL QUALITATIVE STUDY | Using interviews and/or focus groups with both patients and their carers. Potential participants will be identified and consented by the clinical care team.<br>1. *Before start of Stage 1: we will involve patients that would be eligible to participate in stage 1 of the study and their carers.*<br>a. What is the patient's and their family's lived experience of coping with tumour and disorders of social cognition?<br>b. What do the participants feel about the proposed study – what potential barriers and enablers to study participation can they see. This will be used to optimise the intervention before Stage 1.<br>2. *After Stage 1:* we will involve the patients and their carers recruited to Stage 1 of the study. We will explore:<br>a. Experiences of being involved in the study and study interventions?<br>b. How we may improve delivery of interventions and assessments?<br>c. How will we approach future patients to Stage 2 and discuss randomisation?<br>3. *After Stage 2*: we will involve patients and their carers recruited to Stage 2 of the study. We will explore<br>a. How can we improve delivery of this intervention to routine clinical practice to make it acceptable to patients?<br>b. What changes would we need to implement in a larger Phase III trial?<br>c. How do the outcome measures reflect patient experience – is there a discrepancy between changes in outcome measures and what patients experience?<br><br>The parallel qualitative study is optional for both patients and their carers. Separate information sheets and consent forms will be provided. |
| Sample Size | A total of approximately 60 patients. Up to 10 patients taking part in the interview/focus groups before stage 1 (these patients may or may not take part in stage 1), approximately 10 patients in Stage 1 and 38 in Stage 2 (randomised 1:1, 19 receiving the active FACES intervention and 19 receiving the control intervention)<br><br>Patient's carers will also be invited to take part in interviews/focus groups and to complete caregiver Quality of Life forms in Stage 1 and Stage 2. |

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| | Separate information sheets and consent forms will be provided for carers. |
| Summary of eligibility criteria | **Inclusion Criteria:**<br>1. Patients pre-screened as part of the CogENT and SIND studies, scoring 11 or less on the emotional recognition test within the OCS-Bridge screening tool done pre-operatively (consistent with having a deficit pre-operatively)<br>2. Signed informed consent to SCARF-BT study<br>3. Aged 18 years and older<br>4. Imaging evidence of a high-grade glioma as assessed by a neuro-oncology MDT;<br>5. MDT and treating clinician recommend either biopsy or debulking of the tumour;<br>6. Patients scoring 11 or less on the emotional recognition test within the OCS-Bridge screening tool done post-operatively (consistent with having a deficit post-operatively)<br>7. Patient with WHO Performance status 0-2;<br>8. Patient suitable for oncological intervention involving radiotherapy/chemotherapy/ combining radiotherapy and chemotherapy.<br>9. *For qualitative study only:* speaks fluent English as the use of interpreters can alter patients' exact words.<br>10. *For Qualitative Study only*: willing to participate in interviews and/or focus groups.<br><br>**Exclusion Criteria**<br>1. Patients unable to give written consent or lack capacity to consent;<br>2. Patients for palliative/best supportive care only following surgery.<br>3. Pre-morbid developmental or acquired/traumatic neurologic disorder (e.g. autism, stroke or dementia/cognitive impairment);<br>4. Pre-morbid major psychiatric disorder (e.g. schizophrenia);<br>5. Impaired vision and/or hearing that would interfere with task participation (determined by interacting with participant on screening and medical history)<br>6. Impaired facial recognition (i.e. prosopagnosia) using a separate test from the OCS-Bridge screening tool, where a score of ≤5 on immediate assessment of neutral face recognition would suggest a deficit requiring exclusion.<br><br>**Inclusion Criteria for Carers**<br>1. Written informed consent<br>2. Family member/someone they care for with Brain Tumour who is participating in this study |

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| | 3. Able and willing to complete the caregiver Quality of Life questionnaires<br>4. *For Qualitative Study only*: speaks fluent English as the use of interpreters can alter patients exact words.<br>5. *For Qualitative Study only*: willing to participate in interviews and/or focus groups. |
| Study Screening –: | • Informed consent<br>• Post-operative OCS-Bridge screening<br>• Personal details ( Age at registration, Gender assigned at birth)<br>• Handedness<br>• Years in Education<br>• Age at leaving full time Education<br>• Clinical data<br>  • WHO performance status<br>  • Histology of tumour and site of tumour<br>• Medical History (Disease Presentation, use of steroid and anti-epileptics to control symptoms) |
| Patient registration | • Age of registration<br>• Gender at birth<br>• Date of informed consent<br>• Confirmation that eligibility criteria have been met |
| Baseline Study Assessments (<2 weeks post-op) | Study assessments:<br>• DANVA2-AF<br>• TASIT (part 1, EET subtest)<br>• TAS-20<br>• EORTC QLQ30 + BN20<br>• CQOLC |
| Randomisation | • Stage 2 only |
| Study Interventions | • Active Intervention (FACES intervention) – 3 x 1-hourly interventions per week for 3 weeks<br>• Control Intervention (general cognition control intervention) – 3 x 1 hourly interventions per week for 3 weeks<br>For Stage 1 – all patients will receive the active intervention.<br>For Stage 2 - a 1:1 randomisation schedule will be used. Half the patients receiving the active FACES intervention and half receiving the control intervention |
| Post-intervention Study Assessments:<2 weeks before start of | • Study assessments:<br>  • DANVA2-AF<br>  • TASIT (part 1, EET subtest)<br>  • TAS-20 |

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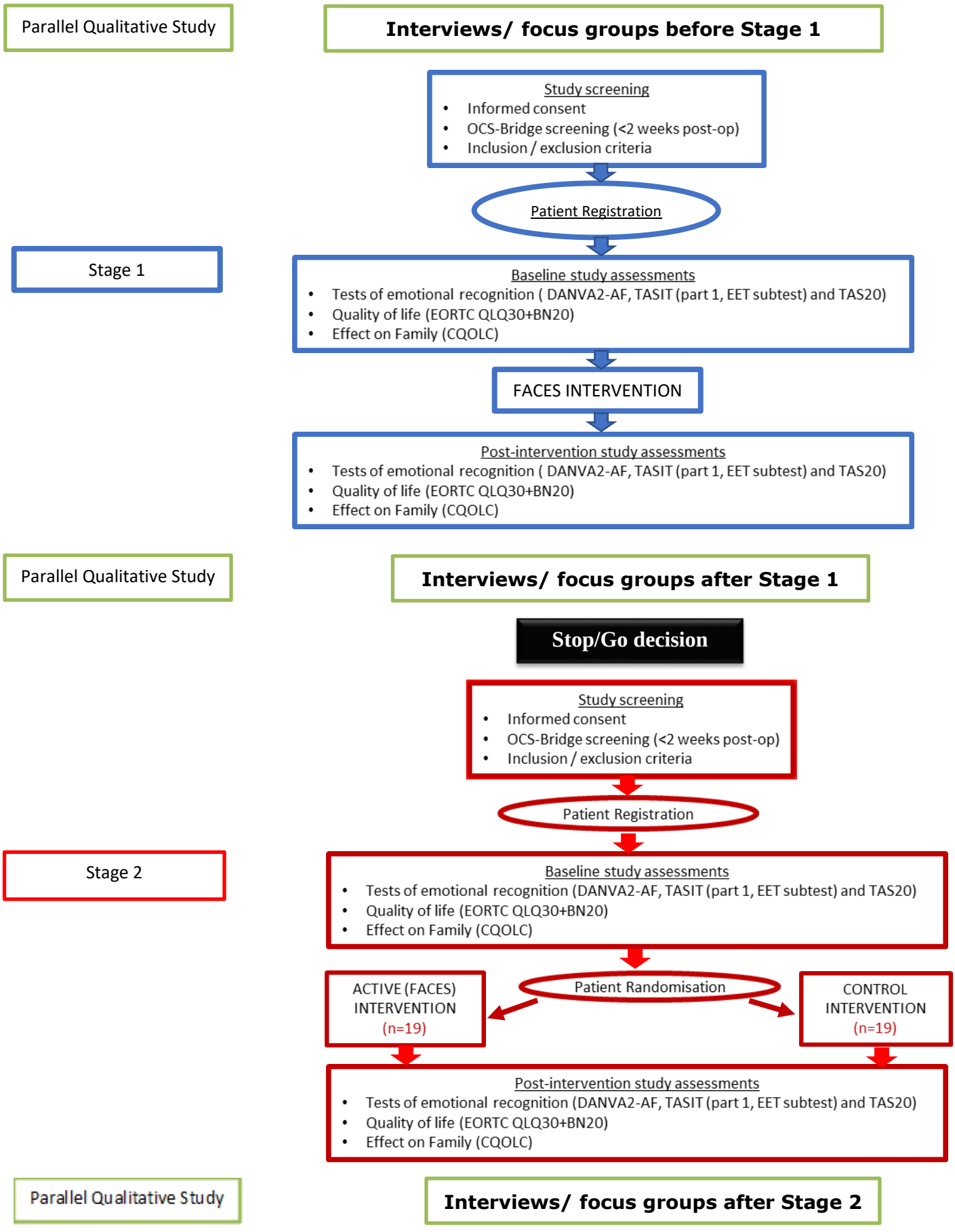
| radiotherapy (usually within 6 weeks of surgery) | • EORTC QLQ30 + BN20<br>• CQOLC |
| End of Study | STAGE 1 will end either; when we understand the intervention and assessments are acceptable to patients and the technique is no longer evolving or; 10 patients have been recruited and undergone their final assessment – whichever is soonest .<br>Although we expect to screen more patients (up to a maximum of 20), we expect to recruit up to 10 patients to go forwards to the intervention at this stage.<br>The Study Management Group will look at the data from the patients completing stage 1 to make a decision whether to stop after stage 1 or to continue to stage 2 (See section 11.2.1)<br><br>STAGE 2 will end when 19 evaluable patients per arm (intervention and control arms) have undergone their final assessment. |
| Criteria for withdrawal of patients | • Patient to be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioural, or administrative reasons.<br>• Patient requests to be withdrawn. |

## 4 Main Study Flow Chart



# 5 Introduction

## 5.1 Background

### *5.1.1 What is the problem being addressed?*

Although less common brain tumours are the commonest cause of cancer death in children, women under the age of 30 and men under the age of 40, for an individual, they lead to the loss of more average years of life than all the common cancers[1]. Most tumours, especially the gliomas, are characterised by invasion of the surrounding brain causing deterioration in quality of life before death. Patients may remain relatively stable for some time before tumour recurrence or progression leads to further brain injury. As all trials of targeted and immunotherapies have failed to provide the benefits seen in other cancers, and as no new treatments are on the horizon, we need to take an approach of 'aggregation of minimal gains' to optimise our existing treatments[2].

The effects of brain tumours on the normal brain function make them different to other cancers. They frequently affect characteristics and faculties that make who we are as individuals: personality, memory, cognition and the ability to interact with others. Changes to an individual's personality and behaviour can make them unrecognisable to friends, loved ones and even themselves, whilst those with speech, memory or concentration problems may find meeting new people stressful and embarrassing. This has an impact on both patients and their family, adversely affecting their functioning and quality of life.

*"The tumour has changed my wife's personality so much I no longer see the person I married and love . . . I feel so alone and trapped".* A Carer

Social cognition is the means by which we perceive, process and interpret social information. It is a fundamental neurocognitive function. The key mechanism for social interaction involves being able to recognise and respond to others' emotions (emotional recognition)[3]. As we primarily communicate our emotions through non-verbal cues, accurate interpretation of facial or vocal expression is essential. In traumatic brain injuries it is well established that the ability to identify emotions from faces[4,5] and other non-verbal cues[6,7] is often significantly compromised. There is also evidence that deficits in emotion perception are related to behavioural problems and poor social outcomes in people with Traumatic Brain Injury[3,8,9]. The inability to know how someone is feeling is likely to result in an inappropriate response, potentially leading to negative interpersonal interactions[5,10] and withdrawal from future social encounters leading to loneliness and isolation[11].

"I am a mother, a daughter, a sister, an employee – I am surrounded by so many yet none of them understand why I can't always recognise them. It is so isolating". A Patient

It is well recognised that following brain injury, the brain is able to 're-organise' to some extent to regain lost function. This brain 'plasticity' allows other brain regions to take over the activities of damaged brain. Rehabilitation aims to help develop this plasticity to minimise the long-term impact of brain injury. Over the years many rehabilitation strategies have been devised for acquired brain injury from trauma and stroke. Rehabilitation programmes for brain tumour patients are very rare, and usually apply methods developed for trauma and stroke injuries to brain tumour patients. Yet the damage to the normal brain is different with tumours. Unlike trauma and stroke where there is a large sudden onset insult and a brief period of secondary/ additionally developing injury, brain tumours demonstrate a more insidious, chronic damage. There is usually a period of undetected tumour invasion of the normal brain, which may be compensated for by the nearby healthy brain tissue. This compensation ability, however, is limited and invasion beyond this can lead to seemingly abrupt and obvious deficits in

function at the time of presentation. There are then episodes of potential brain injury from treatment - surgery especially, but radiotherapy and chemotherapy can also cause damage. This is compounded by the effects of corticosteroids and anticonvulsant drugs given to many patients. It is uncertain whether clinically meaningful brain 'plasticity' can occur in rapidly growing, malignant tumours. In addition, the regular trips to hospital for radiotherapy and the fatigue this causes makes it important that evidence-based home-delivered therapies are available options, and they are acceptable to this patient group. It is therefore important we understand if such rehabilitation strategies will be of benefit for brain tumour patients to improve core functions and in turn, quality of life.

### *5.1.2 Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health care services?*

It is unfortunate, but most patients with brain tumours will not be cured in the foreseeable future. Currently the median survival following maximal therapy is 14-18 months[12]. As a result, we tell our patients that our aim is to maintain their quality of life for as long as we can. To achieve this, our clinical services need to address both improving survival and maintaining quality of life with rehabilitation.

Our data, however, suggests rehabilitation is not available. A survey of patients treated by our service identified only 28% felt they were offered rehabilitation. This rehabilitation focused on physical problems with 52% seeing a physiotherapist, 32% an occupational therapist and 10% a speech and language therapist. Rehabilitation was certainly valuable to patients – 94% found it was useful for them.

Our survey also found that only 20% were offered psychological support. A recent national patient survey suggested only 7% had psychological support and 10% had neuropsychological support, despite 56% stating that it would have been beneficial[13]. Furthermore, a large survey from the Brain Tumour Charity of over 1000 patients found that 91% of patients with a brain tumour felt the tumour had affected their emotional or mental health. This is far greater than the physical symptoms our services are designed to detect and manage. The change in personality, reported in 28% of patients, leads to partners feeling they are 'married to a stranger'. Two in three patients report a negative impact on relationships with their partner – this strain can cause relationship breakdown; where a relationship is sustained it may be altered in every aspect. This impact on social interactions cause major problems, with 70% of patients describing that they felt awkward in social situations leading to 61% participating less social activity. This leads to the patient becoming isolated – 29% describe being severely isolated.

In addition to patient reports, cognitive deficits have also been highlighted on routine cognitive screening. Our initial, unpublished work studied 16 glioblastoma patients at three time points around surgery. All patients were assessed using the OCS-Bridge screening tool (https://ocs-bridge.com/about.html) on a tablet computer. We found that 9/16 patients (56%) had deficits in emotional recognition pre-operatively and this increased to 12/16 (75%) post-operatively. A number of these patients did improve by the start of radiotherapy, but 9/16 (56%) remained impaired – these patients all had deficits pre-operatively. In addition, the reaction time of our patients was on average 500 ms slower than controls. Post-operatively this reaction time was 900 ms slower than pre-operatively suggesting that not only is there a deficit in correct emotion identification, but also that emotional processing is delayed. This delay is critically important as facial expressions are highly dynamic and emotional expressions change rapidly and require rapid processing. These additional processing delays may even be a factor in the general fatigue commonly reported in this patient group. These figures are similar to other published studies[14] and suggest that problems with emotional recognition is a common problem in this patient group.

The heavy burden of these problems and a lack of suitable rehabilitation makes this an area of marked, unmet need.

### *5.1.3 Review of existing evidence*

There is very little published data on the impact rehabilitation has on brain tumour patients. A Cochrane review published in 2015[15] was only able to identify a single study. This small randomised controlled study assessed the effectiveness of a multi-disciplinary rehabilitation programme[16]. This study randomised patients to either intensive ambulatory multidisciplinary rehabilitation (treatment group) or a waiting list for rehabilitation (control group). They showed the rehabilitation had an increase in the Functional Independence Measure (FIM) at three months, and improvements in the 'communication' and 'cognitive' subscales at 6 months. This suggests rehabilitation can improve patient functioning, with some gains maintained for up to six months. The authors did feel it was important to get "evidence for specific interventions in the 'black-box' of rehabilitation".

A study in patients with traumatic brain injury has shown that emotional recognition training, delivered using a computer-aided intervention, improves emotional recognition compared to a control group[17]. Their FACES INTERVENTION teaches participants to recognise emotions from facial expressions using 3 main learning concepts:

to attend to relevant facial features and associate these features with specific emotions;

to increase awareness of one's own emotions through introspection and imitation so that participants could use their emotional experience to better recognize others' emotions, and to develop associative knowledge and a better conceptual understanding of emotions.

These changes were maintained to at least 6 months[17]. As mentioned previously, the pattern of brain injury with brain tumours is different, so it is not yet known if this intervention would work in brain tumour patients. The intervention focuses on multiple learning concepts that target the 3 main mechanisms of emotion recognition, this comprehensive approach may help to improve areas that were impaired, and further strengthen areas that were not impaired. We hypothesise that the intervention would improve emotional recognition in brain tumour patients to some extent. At present there is no other, specific intervention that has been shown to work in brain tumour patients. For these reasons, this is the intervention we plan to evaluate in this study. Such a rehabilitation strategy could be performed by patients in their homes with little resources and thus could easily become a widespread treatment for patients, within a short time frame.

## 6 Rationale for Study

Our ultimate aim is to develop a tailored clinical service that can provide evidence-based rehabilitation strategies to treat common emotional and cognitive problems. This RfPB application is a feasibility study for one such intervention targeted at one important and common problem – namely emotional recognition. We aim to assess if we can screen for these problems, provide an intervention, and a method of assessment to evaluate this intervention, and ensure this intervention is acceptable to patients.

It is important to identify patients with pre-existing defects of emotional recognition pre-operatively as a further 20% of patients acquire temporary deficits post-operatively. Whereas our data from the CogENT study suggests patients with deficits pre-operatively do not improve at delayed assessment. This method of identifying potential patients will therefore help exclude patients that may get better without any rehabilitation. Patients scoring 11 or less on the emotional recognition test that are part of the OCS-Bridge battery are considered to have a deficit.

# 7 Study Design

## 7.1 Statement of design

This is a two-stage feasibility study with a parallel qualitative study.

STAGE 1: a cohort study
STAGE 2: a placebo-controlled feasibility randomised controlled trial

Parallel qualitative study: using interviews and/or focus groups at three stages:

- Before start of study
- After Stage 1
- After Stage 2

## 7.2 Number of Centres

This trial will be conducted in a minimum of one institution in the UK, run at Cambridge University Hospitals NHS Foundation Trust. Our preliminary data has shown steady recruitment and retention longitudinally at one site (Cambridge University Hospitals NHS Trust) in the CogENT study.

## 7.3 Number of Patients

We plan to include a total of approximately 60 patients in this study. Up to 10 patients will take part in interviews prior to Stage 1, approximately 10 in Stage 1 and 38 in Stage 2 (randomised 1:1; 19 receiving the active FACES intervention and 19 receiving the control intervention.)

We will also be inviting patient's carers to take part in interviews/focus groups and to complete a caregiver Quality of Life form forms in Stage 1 and Stage 2.
Separate information sheets and consent forms will be provided for carers.

## 7.4 Participants Study duration

Patients will participate in the study until the post intervention study assessments which will be performed prior to commencing radiotherapy (approximately six weeks following surgery).

## 7.5 Study objectives

This is a feasibility study and as such our objectives relate to feasibility.

### *7.5.1 Stage 1: the cohort study*

The specific objectives for this part of the study are:

1. To examine if patients are able to complete the intervention with the support of a psychologist (defined as completing all 9 sessions of training).
2. To study, document and understand the iterative changes of a new technique for delivering a rehabilitation intervention (FACES – computer based training programme) and provide a narrative account of these changes until a stable technique has been developed (as described for Stage 2a IDEAL interventions[18]).
3. To assess acceptability of intervention as part of the parallel qualitative study.

4. Feasibility of assessment completion by recording established validated outcome assessments patients are able to complete
5. Feasibility of quality of life completion by both patient and carer

*7.5.2 Stage 2: placebo-controlled feasibility randomised controlled trial*

The specific feasibility objectives for this stage will be:

1. To explore if we are able to screen patients for deficits in emotional recognition using OCS-Bridge (https://ocs-bridge.com/about). This is a tablet-based neuropsychological screening tool that uses three sets of tests (a) the Oxford Cognitive Screen (OCS) that assess language, semantics, orientation, reading, movement, number knowledge, mental flexibility, spatial attention and memory. (b) the Cambridge Attention, Memory and Perception Screen, and (c) standardised tests of mood (PHQ-9 and GAD-7)
2. To assess acceptability of the intervention, based on patients meeting the eligibility criteria that give consent for the study. This will be explored further as part of the parallel qualitative study.
3. To assess the ability to complete the active FACES intervention and control intervention.
4. To assess the acceptability of a number of established, validated outcome assessments as part of the parallel qualitative study.
5. To assess the impact on patient reported quality of life.
6. To assess the impact on patient's families.
7. To compare the impact of the active FACES intervention with the control intervention on scores for selected assessments.

*Parallel Qualitative Study*

Using interviews and/or focus groups involving both patients and their carers. Participation in the qualitative study is optional for both patients and their carers. Separate participant information and consent forms will be used. A patient may take part without their carers participation at any stage of this study. A carer may take part without the participation of the patient for the initial interviews/focus groups before stage 1 (pre-intervention) only.

The objectives for this parallel study running through both stages of the study are:

1. To explore the experiences and perspectives of people with tumour, and carers regarding their lived experience and the perceived importance of the proposed intervention.
2. To explore their experiences of the intervention including preferred/suitable intervention content and delivery formats, experience of randomisation and potential barriers and facilitators to intervention delivery.
3. Perceptions of outcome measures and whether they capture the issues of importance to people completing the intervention.

4. To explore the experiences and perspectives of health care professionals regarding their experiences of delivering the intervention and potential barriers and facilitators to further delivery of the intervention within routine clinical services.

## 7.6 Study Outcome Measures

*7.6.1 Stage 1: the cohort study*

The specific outcome measures for this part of the study are:

1. Percentage of patients completing the intervention (defined as completing all 9 sessions).
2. Prospective recording of any changes to the administration, conduct and content of the rehabilitation intervention on a patient-by-patient basis.
3. The acceptability of the intervention will be explored through a parallel qualitative study (see below 7.6.3).
4. Percentage of patients completing the following validated outcome assessments
   a. Diagnostic Assessment of Non-verbal Accuracy-2, Adult Faces (DANVA2-AF);
   b. Emotion Recognition and Social Inference: The Awareness of Social Inference Test (TASIT), (part 1, EET subtest);
   c. The Toronto Alexithymia Scale-20 (TAS-20).
5. Percentage of patients and carers able to complete quality of life questionnaires.

*7.6.2 Stage 2: placebo-controlled feasibility randomised controlled trial*

The outcome measures for this stage will be:

1. We will record the number of patients who undergo screening (the numerator) and the number of potentially eligible patients that attend clinic (the denominator). To proceed with a larger, efficacy study we would need to be able to use OCS-Bridge to screen a minimum of 75% of new patients.
2. The percentage of screened patients meeting the eligibility criteria provide informed consent for the study. It will also be explored in more detail with the qualitative study (see below).
3. Percentage of patients who have completed all sessions for the FACES intervention (active intervention) and General Cognition Intervention (control intervention). To proceed to further studies this will again need to exceed 80%.
4. We will measure completion rates for the following established, validated outcome assessments pre- and post-intervention.
   a. Diagnostic Assessment of Non-verbal Accuracy-2, Adult Faces (DANVA2-AF);
   b. Part 1, which includes emotion recognition, of Emotion Recognition and Social Inference: The Awareness of Social Inference Test (TASIT);
   c. The Toronto Alexithymia Scale-20 (TAS-20).

   Acceptability will be explored with our parallel qualitative study.

5. Patient reported quality of life using the EORTC QLQ-30 with the BN20 brain tumour module[19].
6. The impact of these problems on patient's families by asking interested family members to complete the Caregiver Quality of Life Index-Cancer (CQOLC).
7. We will calculate the difference in scores pre and post intervention for the selected assessments (see above) for both the active (FACES) intervention group and the control group. This will provide an early indicator that the intervention may make some difference and would be worth exploring in a larger, multicentre study as well as determining future sample sizes.

### *7.6.3 Parallel Qualitative Study*

Using interviews and/or focus groups with both patients and their carers.
Three time points will be studied – for each time point specific questions will be explored:

1. *Before start of stage 1:* we will involve patients that would be eligible to participate in stage 1 of the study and their carers. We will explore the following topics:
    a. What is the patient's and their family's lived experience of coping with tumour and disorders of social cognition?
    b. What do the potential participants feel about the proposed study – what potential barriers and enablers to trial participation can they see. This will be used to optimise the intervention before Stage 1.
2. *After Stage 1:* we will involve the patient group recruited to Stage 1 of the study and their carers. We will explore:
    a. Experiences of being involved in the study and study interventions?
    b. How we may improve delivery of interventions and assessments?
    c. How will we approach future patients to Stage 2 and discuss randomisation?
3. *After Stage 2*: we will involve patients recruited in Stage 2 of the study and their carers. We will explore:
    a. How can we improve delivery of this intervention to routine clinical practice to maximise its acceptability to patients?
    b. What changes would we need to implement in a larger Phase III trial?
    c. How do the outcome measures reflect patient experience – is there a discrepancy between changes in outcome measures and what patients experience?

Participation in the qualitative study is optional for both patients and their carers. A patient may take part without their carers participation at any stage of this study. A carer may take part without the participation of the patient for the initial interviews/focus groups before stage 1 (pre-intervention) only. Separate information sheets and consent forms will be provided.

## 8 Selection and withdrawal of subjects

### 8.1 Inclusion Criteria

Patients recruited to this study will require the following inclusion criteria:

1. Patients pre-screened as part of the CogENT and SIND studies, scoring 11 or less on the emotional recognition test within the OCS-Bridge screening tool done pre-operatively (consistent with having a deficit pre-operatively)
2. Signed Informed Consent to SCARF-BT study
3. Aged 18 years and older
4. Imaging evidence of a high-grade glioma as assessed by a neuro-oncology MDT;
5. MDT and treating clinician recommend either biopsy or debulking of the tumour;
6. Patients scoring 11 or less on the emotional recognition test within the OCS-Bridge screening tool done post-operatively (consistent with having a deficit post-operatively)
7. Patients with WHO Performance status 0-2;
8. Patients suitable for oncological intervention (involving radiotherapy/ chemotherapy/ combining radiotherapy and chemotherapy);
9. *For Qualitative Study only:* speaks fluent English as the use of interpreters can alter patients exact words.
10. *For Qualitative Study only*: willing to participate in interviews and/or focus groups.
11.

### 8.2 Exclusion Criteria

The presence of any of the following will preclude patient inclusion:

1. Patients unable to give written consent or who lack capacity to consent;
2. Patients for palliative/best supportive care only, following surgery.
3. Pre-morbid developmental or acquired/traumatic neurologic disorder (e.g. autism, stroke, severe head injury or dementia/cognitive impairment);
4. Pre-morbid major psychiatric disorder (e.g., schizophrenia);
5. Impaired vision and/or hearing that would interfere with task participation (determined by interacting with participant on screening and medical history);
6. Impaired facial recognition (i.e. prosopagnosia) using a separate test from the OCS-Bridge screening tool, where a score of ≤5 on immediate assessment of neutral face recognition would suggest a deficit requiring exclusion.

### 8.3 Inclusion Criteria for Carers

1. Written informed consent
2. Family member/someone they care for with Brain Tumour who is participating in this study
3. Able and willing to complete the caregiver Quality of Life questionnaire

4. *For Qualitative Study only*: speaks fluent English as the use of interpreters can alter patients exact words.
5. *For Qualitative Study only*: willing to participate in interviews and/or focus groups.

### 8.4 Subject withdrawal criteria

Patients may withdraw from the trial assessments or from the trial completely, at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioural, or administrative reasons.

If the patient withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The Study Management Group (SMG) may retain and continue to use any data collected before such withdrawal of consent.
Patients should be withdrawn from the study and replaced only if the patient requests to be withdrawn.

## 9 Procedures and assessments

Summary of the timings and assessments is listed below in the table - Section 9.9.

### 9.1 Patient identification

Patients that will be approached for this study will have already been recruited for one of the two studies detailed below. They will have had a cognitive screen using the OCS-Bridge screening battery as part of either:

1. The Cognition Evaluation for patients with Neurological Tumours (the CogENT study) - REC reference: 18/LO/0491.
2. Assessing impact of surgically-induced deficits on patient functioning and quality of life (SIND study) - REC reference: 19/WM/0152.

Patients will be identified pre and post operatively from our Multi-Disciplinary Team (MDT) process.

It is important to identify patients with pre-existing defects of emotional recognition pre-operatively as a further 20% of patients acquire temporary deficits post-operatively. Whereas our data from the CogENT study suggests patients with deficits pre-operatively do not improve at delayed assessment. This method of identifying potential patients will therefore help exclude patients that may get better without any rehabilitation. Patients scoring 11 or less on the emotional recognition test that are part of the OCS-Bridge battery are considered to have a deficit.

Patients will be approached either in a clinic or remotely by telephone (in accordance with Trust guidance concerning COVID-19). The study will be introduced to the patient and they will be provided with the patient information sheet. Patients will be given time to think about participating and will be followed up by phone call/further phone call. Patients who wish to take part will then be invited to give written consent at their next clinic visit. The patient's carers will also be approached about completing their own assessments. Carers who wish to take part will give written informed consent.

## 9.2 Study Screening

Only after the patient has consented to participate can the study specific assessments be performed.

The following assessments are required at screening:

- Informed consent
- Post-operative OCS-Bridge screening
- Personal details (Age at registration, Gender assigned at birth)
- Handedness
- Years in Education
- Age at leaving full time Education
- Clinical data:
    - WHO performance status (Refer to Appendix 2)
    - Histology of tumour and site of tumour
- Medical History (Disease Presentation, use of steroid and anti-epileptics to control symptoms)

## 9.3 Patient Registration

Registration of eligible patients will be performed prior to any baseline research assessments taking place. To register patients the delegated study team member will be required to, at a minimum, provide the following information:

- Age at registration
- Gender assigned at birth
- Date of informed consent
- Confirmation that eligibility criteria have been met

A unique patient identifier will be allocated for each individual patient.

## 9.4 Study assessments - Baseline

Post-operative assessments should be carried out within two weeks of surgery, and only after the patient has been registered these include:

1. Diagnostic Assessment of Non-verbal Accuracy-2, Adult Faces (DANVA2-AF)[20] – a computerised test showing 24 photographs of 4 different facial expressions for 2.5 seconds each. Normative scores are available by age for this measure and an abnormal score is defined as ≥1 Standard deviation from the norm).
2. Part 1 of Emotion Recognition and Social Inference: The Awareness of Social Inference Test (TASIT) uses short one-minute video vignettes to assess emotion and social inferences. There are three subtests that comprise the TASIT: Emotional Evaluation Test (EET); the Social Inference-Minimal (SI-M); and Social Inference-Enriched (SI-E), but only the EET subtest will be used in this study. In the EET subtest, actors portray seven different emotions with dynamic facial movements, tone of voice, postures and gestures through short vignettes. These emotions include happy, sad, angry, disgust, fearful, surprised and neutral. We will use data from the EET subtest for our analyses As A and B tests exist, we will use both tests to avoid learning effect.
3. The Toronto Alexithymia Scale-20 (TAS-20) – this is the most widely used self-reported questionnaire to measure alexithymia and is comprised of 3 factors: 1)

ability to identify emotions (e.g., I am often confused about what emotion I am feeling); 2) ability to describe emotions (e.g., It is difficult for me to find the right words for my feelings); and 3) externally-oriented thinking (e.g., I prefer to just let things happen rather than understand why they turned out that way).

4. Patient reported quality of life.(EORTC QCQ30 with the BN20)
5. Patient's families quality of life (Caregiver Quality of Life Index-Cancer (CQOLC)http://www.midss.org/content/caregiver-quality-life-index-cancer-cqolc-scale.

Quality of life questionnaires will be completed before the clinic visit. If patients or their carers become distressed by the topics raised in the quality of life questionnaires, they will be supported by members of the clinical research team during their clinic visit.

Stage 1 will be used to define which of the assessments patients are able to complete. These assessments will be used for stage 2.

## 9.5 Randomisation

STAGE 1: This is a non-randomised study. All patients will undergo the FACES Intervention

STAGE 2: Patients will be randomised 1:1; half receiving the FACES intervention (active intervention) and the other half receiving the General Cognition Intervention (control intervention)
'A web-based central randomisation system supplied by Sealed Envelope will allocate the intervention.

## 9.6 Study Interventions

For both patient cohorts training on the use of the interventions will be provided. In Stage 1 all patients will receive the FACES intervention. In Stage 2 patients will be randomised to either FACES intervention or General Cognition Control Intervention.

Where necessary a computer will be provided to patients for the duration of the study to allow them to do the interventions.

### *9.6.1 FACES Intervention (active intervention)*

This intervention has been previously described and validated in patients with traumatic brain injury[17]. In essence, the intervention will be a one-to-one computer-assisted treatment facilitated by an assistant psychologist who will have received training in administering the test. It will consist of 3 x 1-hour interventions each week for 3 weeks. This will be started post-operatively and continued until they start other treatments such as radiotherapy.

The program is designed so that difficulty is gradually increased throughout the intervention by using facial expressions ranging from obvious to subtle and through the use of vanishing cues (i.e., cues to guide participants' attention).

### *9.6.2 General Cognition Control Intervention (control intervention)*

The purpose of the cognitive training intervention was to control for the one-on-one attention and personal interaction that participants in the treatment groups were

receiving, without providing any type of emotion-related training. Previous studies have confirmed a 'placebo effect' and the necessity of a control intervention[17]. Participants in Cognitive Training played a variety of online, publicly available computer games that targeted speed of processing, visual scanning, attention, memory, reasoning, and problem-solving skills.

## 9.7 Study Assessments - Post-Intervention

These assessments will be performed before the start of radiotherapy and after completing the three weeks of the intervention. Time points later than this will be confounded by effects of radiotherapy. These assessments will include:

1. Diagnostic Assessment of Non-verbal Accuracy-2, Adult Faces (DANVA2-AF);
2. Part 1 (EET subtest) of Emotion Recognition and Social Inference (TASIT);
3. The Toronto Alexithymia Scale-20 (TAS-20).
4. Patient reported quality of life.(EORTC QCQ30 with the BN20)
5. Patient's families quality of life.(Caregiver Quality of Life Index-Cancer (CQOLC). http://www.midss.org/content/caregiver-quality-life-index-cancer-cqolc-scale

Quality of life questionnaires will be completed before the clinic visit. If patients or their carers become distressed by the topics raised in the quality of life questionnaires, they will be supported by members of the clinical research team during their clinic visit.

Stage 1 will be used to define which of the assessments that patients are able to complete. These assessments will be used for stage 2.

## 9.8 Parallel Qualitative Study

A patient may take part without their carers participation at any stage of this study. A carer may take part without the participation of the patient for the initial interviews/focus groups before stage 1 (pre-intervention) only. Separate information sheets and consent forms will be provided.

### *9.8.1 Qualitative Study Methodology*

To ensure the proposed intervention and outcome measures are meaningful for people with brain tumours, we will undertake one-to-one interviews and/or focus groups. We have opted for both interviews and focus groups, where feasible, to offer participants choice and because both formats provide complementary but different data[21]. These will investigate both the experience of the intervention and suggestions for the recruitment, content and delivery format for an intervention. Interview schedules and topic guides will be drawn from PPI advice, the literature presented above and work from the Oliver Zangwill Centre on measuring patient-centred outcomes.

Participants will be approached to take part in the parallel qualitative study and information sheets provided by a member of the clinical care team. Initial agreement to be contacted about participating in interviews and focus groups will be obtained by a member of the clinical care team. This will include contact details of the potential participants to enable the qualitative researcher to discuss participation and obtain written informed consent.

A minimum recommended sample size for qualitative interviews with homogenous groups is 12 [22]. Data collection will cease when data saturation is reached (defined as where no

information is generated to change or add to existing themes)[22]. Based on previous research, we expect data saturation with this sample size. Up to three focus groups may be run comprising 6-8 participants to enable people to feel comfortable to share their experiences focus discussion on the required topics[23].

A variation of methods will be used for the interviews and focus groups including: face-to-face, telephone or videoconference. If face-to-face method is used, focus groups will be run in three locations across East Anglia (Ipswich, Norwich and Cambridge) to ensure geographical location is not a barrier and reasonable travel expenses will be reimbursed; telephone and videoconference interviews can be completed to compensate for fatigue or to meet current Trust Guidance for example during the COVID 19 pandemic. Interviews will last up to 60 minutes and focus groups up to 90 minutes depending on patient/carer preference, need for breaks and fatigue.

To ensure accuracy interviews and focus groups will be recorded and stored on an NHS shared drive accessible on an encrypted password protected NHS computer. Participants will be required to consent to this recording and will be instructed not to disclose personally identifiable information (such as their or other's names) but, if they do, these will be edited out (researchers to note if this occurs and the time on the recorder to facilitate edits). Recordings will be transcribed by the lead qualitative researcher who is an NHS clinical psychologist. Anonymised transcriptions of the interviews and focus groups may be shared with other researchers and anonymised direct quotes, from which participants cannot be identified, may be used in any scientific publications, presentations to clinicians, other scientists, the public or press. Recordings will be destroyed after the study results have been analysed. Anonymised transcripts will be kept and stored as part of the study data.

Interviews and focus groups with the research therapist and other staff involved in delivering the intervention will be performed in collaboration with our PPI advisors and supported by Brainstrust (https://brainstrust.org.uk) who have agreed to match the funding for these sessions. PPI advisors will provide service user representation and will be trained in the research method.

### *9.8.2 Timing of Focus Groups/Interviews*

The focus groups/interviews will be undertaken at three stages of this project. Each will have specific objectives and aims:

1. *Before start of study:* we will involve patients that would be eligible to participate in stage 1 of the study and their carers. this group will explore the following topics:
    a. What is the patient's and their family's lived experience of coping with disorders of social cognition?
    b. What do the participants feel about the proposed study – what potential barriers and enablers to trial participation can they see. This will be used to optimise the intervention before Stage 1.
2. *After Stage 1:* we will involve the patient group (including carer/family member) that had been recruited to Stage 1 of the study. We will explore:
    a. Experiences of being involved in the study and study interventions?
    b. How we may improve delivery of interventions and assessments?
    c. How will we approach future patients to Stage 2 and discuss randomisation?
3. *After Stage 2*: we will involve the patient group (including carer/family member) that had been recruited to Stage 2 of the study. We will explore:

a. How can we improve delivery of this intervention to routine clinical practice to make it acceptable to patients?
b. What changes would we need to implement in a larger Phase III trial?
c. How do the outcome measures reflect patient experience – is there a discrepancy between changes in outcome measures and what patients experience?

*9.8.3 Analysis*

Data will be analysed via a qualitative method such as constant comparison analysis[24]. The research team have expertise in developing interventions for people with neurological conditions and corresponding feasibility studies. An intervention will be developed based on knowledge from these prior interventions, and findings from interviews and focus groups with relevant stakeholders.

## 9.9 End of Study Participation

Patients will return to the normal standard of care once the Delayed Post-Operative Assessment is completed.

At the end of the study the patient and their family will be offered a final feedback session to explain the patient's problems and discuss possible strategies for dealing with these issues.

Participants will be offered a summary of the study findings.

## 9.10 Schedule of Assessments

| Time Point | Study Screening | Registration | Baseline | Randomisation[4] | INT-1 | INT-2 | INT-3 | INT-4 | INT-5 | INT-6 | INT-7 | INT-8 | INT-9 | Post -INT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Time Frame** | **<2 weeks post-op** | | **<2 weeks post-op** | | **Week 1** | **Week 1** | **Week 1** | **Week 2** | **Week 2** | **Week 2** | **Week 3** | **Week 3** | **Week 3** | **< 2 weeks before radiotherapy** |
| **Consent** | X | | | | | | | | | | | | | |
| **OCS-Bridge screening[1]** | X | | | | | | | | | | | | | |
| **Medical History[2]** | X | | | | | | | | | | | | | |
| **Clinical data[3]** | X | | | | | | | | | | | | | |
| **DANVA2-AF[5]** | | | X | | | | | | | | | | | X |
| **TASIT[6]** | | | X | | | | | | | | | | | X |
| **TAS-20[7]** | | | X | | | | | | | | | | | X |
| **QoL questionnaire[8]** | | | X | | | | | | | | | | | X |
| **Instruct patient[9]** | | | X | | | | | | | | | | | X |
| **INTERVENTION[10]** | | | | | X | X | X | X | X | X | X | X | X | |
| **Patient feedback[11]** | | | | | | | | | | | | | | X |

1. Potential patients will be identified pre-operatively (as part of CogENT and SIND studies) for deficits using the OCS-Bridge screening tool., After consent, the OCS-Bridge screening tool will be used post-operatively during screening to ensure deficits remain
2. Medical history will include disease presentation, pre-existing neurological, psychiatric or hearing or visual problems that will prevent testing.
3. Clinical data will include performance status, histology of tumour, site of tumour.
4. Randomisation – Stage 2 only
5. DANVA2-AF = Diagnostic Assessment of Non-verbal Accuracy-2, Adult Faces.
6. TASIT = The Assessment of Social Interference Test (Part 1)
7. TAS-20 = Toronto alexithymia scale.
8. Quality of life will be assessed using the EORTCQLQ-30 scale with the BN20 brain tumour module
9. Patients will be instructed to use the intervention – a patient manual is available.
10. Intervention is either the Emotional Recognition Rehabilitation Intervention – the Faces Intervention or General Cognition Control Intervention
11. A final patient feedback session will be offered to explain the patient's problems and strategies for dealing with this

# 10 Assessment of Safety

## 10.1 Definitions

*10.1.1 Adverse Event (AE)*

Any untoward medical occurrence in a patient or clinical trial which does not necessarily have a causal relationship with the study procedure.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with study procedures, whether or not considered related to the study procedure.

*10.1.2 Serious Adverse event (SAE)*

Any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect; or
- Is otherwise considered medically significant by the investigator - Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/ consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious'.

Life-threatening in the definition of a serious adverse event refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

## 10.2 Expected Adverse Events for this study

We do not expect any adverse events related to the study assessments or interventions.

## 10.3 Evaluation of Adverse Events

Only Serious Adverse Events (SAEs) as defined in section 10.1.2 that are suspected to be related to study procedures will be collected.

*10.3.1 Assessment of seriousness*

Seriousness is assessed against the criteria in section 10.1. This defines whether the event is an adverse event or a serious adverse event.

*10.3.2 Assessment of causality*

Definitely: A causal relationship is clinically/biologically certain.

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and study procedures and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and study procedures.

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible.

Unlikely and Unrelated causalities are considered NOT to be related to study procedures

Definitely, Probable and Possible causalities are considered to be related to study procedures.

A pre-existing condition must not be reported as an SAE unless the condition worsens during the trial and meets the criteria for reporting or recording in the appropriate section of the CRF.

*10.3.3 Assessment of severity*

All SAEs experienced will be graded for severity according to the NCI CTCAE Toxicity Criteria (Version 4.03). CTCAE v4.03 can be downloaded from the following URL: http://ctep.cancer.gov/reporting/ctc.html

### 10.4 Reporting of SAEs

Only SAEs that are **possibly, probably or definitely** related to the study procedures will be recorded and reported.

The Principal Investigator needs to report all Serious Adverse Events which are **possibly, probably or definitely related** to the study procedures using the trial specific SAE form within 24 hours of their awareness of the event.

The Chief Investigator or his deputy is responsible for ensuring the assessment of all reported SAEs for expectedness and relatedness is completed and the onward notification of all related SAEs to the Sponsor immediately but not more than 24 hours of first notification.

If the SAE is deemed to be **related** and **unexpected** (i.e. not listed in section 10.2), it must be notified to the Research Ethics Committee within 15 days of first notification from the site using the Health Research Authority report of Serious Adverse Event form (see HRA website).

In the case of an SAE which is possibly, probably or definitely related to the study procedures, the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal or the disease has stabilised.

The completed SAE form can be emailed. Details of where to report the SAE's can be found on the front cover of the protocol.

## 11 Statistics

### 11.1 Number of patients

Up to 10 patients and their carers will be involved in interviews and/or focus groups prior to stage 1.

*11.1.1 Stage 1*

No formal sample size calculations were performed for Stage 1. Stage 1 will end either; when we understand the intervention and assessments are acceptable to patients and the technique is no longer evolving or; 10 patients have been recruited and undergone their final assessment – whichever is soonest.

Although we expect to screen more patients (up to a maximum of 20), we expect to recruit up to 10 patients to go forwards to the intervention at this stage.

*11.1.2 Stage 2*

For this study, our baseline scenario is where an uptake of above 50% or higher would seem acceptable while an uptake of the proposed intervention below 50% would be deemed unacceptable. With standard choices for significance level of 0.05 and a power of 80%, we would need a sample size of at least 19 subjects per arm to demonstrate feasibility

Acceptability/feasibility will be concluded if at least 50% of patients complete the proposed intervention. Assuming a significance level of 5%, 19 subjects in each arm would provide 80% power to observe at least 50% difference between the active FACES intervention and the control intervention.

*11.1.3 Parallel Qualitative Study*

- Before start of study this will involve up to 10 patients and their carers
- After Stage 1 to include patients and their carers participating in Stage 1
- After Stage 2 to include patients and their carers participating in Stage 2

## 11.2 Statistical methods

*11.2.1 Stage 1- **Criteria for Stop/Go decision prior to Stage 2***

At the end of Stage 1 there will be an assessment made by the SMG as to whether the Stage 2 study should go ahead. This decision will be made on the following criteria:

1. Percentage of patients attending the Surgical Neuro-oncology Clinic that are screened for emotional recognition deficits pre-operatively?
2. Percentage of patients with a deficit that are approached for the study?
3. Percentage of patients recruited that can complete all the assessments?
4. Percentage patients recruited that are able to complete the FACES intervention adapted for remote delivery with the assistance of a psychologist.

As per the sample size calculations described above, less than 50% would be deemed unacceptable (see Sample Size calculation above).

*11.2.2 Stage 2 -**Feasibility Assessments***

1. To explore if we are able to screen patients with suspected high grade glioma attending clinic for deficits in emotional recognition. A deficit in emotional recognition is defined as scoring 11 or less on the emotional recognition test from the OCS-Bridge battery. To proceed with a larger, efficacy study we would need to be able to screen a minimum of 75% of new patients.
2. Acceptability will be assessed by calculating the percentage of screened patients that provided informed consent. The intervention will be considered feasible if at least 50% of patients meeting the eligibility criteria provided informed consent. This will be explored in more detail with the parallel qualitative study.
3. To Assess the compliance of the intervention and control arms, the percentage of patients who have completed all sessions will be calculated. Compliance will be concluded if at least 80% of patients complete all sessions.
4. Assess the acceptibility of the following established, validated outcome measures:
    a. Diagnostic Assessment of Non-verbal Accuracy-2, Adult Faces (DANVA2-AF);
    b. Part 1, which includes emotion recognition, of Emotion Recognition and Social Inference: The Awareness of Social Inference Test (TASIT);

c. The Toronto Alexithymia Scale-20 (TAS-20).

For each of these measures we will measure completion rates pre- and post-intervention. Acceptability will be explored further with our parrallel qualitative study.

5. To Assess the effect size of the intervention we will be assess changes in assessment measures (below) between the active (FACES) intervention group and the control group. Differences in scores will be assessed for:
   a. DANVA 2-AF
   b. TASIT – using the TASIT version B at retest.
   c. TAS-20 alexithymia.
   d. QLQ30 and BN20 quality of life measures will be assessed using published minimal clinically important differences[25].
6. The difference between the Intervention group and the control group in Outcome Measures will be calculated together with 95% confidence interval. This will provide an early indicator that the intervention may make some difference and would be worth exploring in a larger, multicentre study as well as determining future sample sizes.

*11.2.3 Parallel Qualitative study*

These quantitative measures will be supported by the qualitative results of the lived experience from patients and carers at interview and focus group discussions

### 11.3 Procedure to account for missing or spurious data

Missing data will be reported and the impact of missing data will be discussed and sensitivity analyses reported according to published standards[26]. The missing data mechanism will be explored and multiple imputation may be applied as a sensitivity analysis compared to a complete case analysis as appropriate. Other sensitivity analyses will be performed in order to evaluate the robustness of the primary analyses.

### 11.4 Definition of the end of the study

STAGE 1 will end either; when we understand the intervention and assessments are acceptable to patients and the technique is no longer evolving or; 10 patients have been recruited and undergone their final assessment – whichever is soonest .

Although we expect to screen more patients (up to a maximum of 20), we expect to recruit up to 10 patients to go forwards to the intervention at this stage.
The Study Management Group will look at the data from the patients completing stage 1 to make a decision whether to stop after stage 1 or to continue to stage 2 (See section 11.2.1)

STAGE 2 will end when 19 evaluable patients per arm (intervention and control arms) have undergone their final assessment.

## 12 Data handling and record keeping

### 12.1 CRF

All data will be transferred into an electronic Case Report Form (eCRF) and will be anonymised when extracted for analysis. All study data in the CRF must be extracted from and be consistent with the relevant source documents. The CRFs must be completed

by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness, and accuracy of the CRF pages. The CRF will be accessible to study coordinators, data managers, the investigators, Clinical Study Monitors, Auditors and Inspectors as required.

Data should be entered into the secured, study database within 28 days of the patient visit being completed.

### 12.2 Source Data

To enable peer review, monitoring, audit and/or inspection the investigator must agree to keep records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples) and all original signed informed consent forms.

### 12.3 Data Protection & Patient Confidentiality

All investigators and study site staff involved in this study must comply with the requirements of the Data Protection Act 2018 and Trust Policy with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Every patient will be allocated a unique identifier that will link all of the clinical information held about them on the study database. It will also be used in all correspondence with participating clinical study sites. At no point in presentations or publications of study data will individual patients be identified.

The collection of the patients NHS number is a requirement and will be collected for the purpose of ensuring that the patient information can be accurately tracked and accessed where necessary. This information will be stored by the coordinating centre in a separate folder to trial documents. All identifiable patient information will be stored in encrypted form within the database, and access limited to the research team at the co-ordinating centre.

To ensure accuracy interviews and focus groups will be recorded. Recordings will be anonymised. Any direct quotes used will also be anonymised, so that patients cannot be identified in any publications. Any recording will be destroyed once the study analysis has been completed. Transcripts from these recordings will be anonymised and stored with the study data.

## 13 Study Management Group

### 13.1 Study Management Group (SMG)

A Study Management Group (SMG) will be formed comprising the Chief Investigator, other co-investigators and contributors (clinical and non-clinical), a member of the PPI advisory group and members of the Cambridge Cancer Trials Unit.

The SMG will be responsible for the day-to-day running and management of the study and will meet approximately 3 times a year but may have more frequent and regular teleconferences in between if it is deemed necessary.

# 14 Ethical & Regulatory considerations

## 14.1 Consent

The Informed Consent form must be approved by REC and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator must ensure that each study participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with their participation.

The investigator will obtain written informed consent from each patient and the patient's carer/family member before any study-specific activity is performed. The informed consent form used for this study and any change made during the course of this study, must be prospectively approved by the REC. The investigator will retain the original of each patient's and their carer/family member signed informed consent form.

Should a patient require a verbal translation of the study documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators.

Any new information which becomes available, which might affect the patient's willingness to continue participating in the study will be communicated to the patient as soon as possible.

## 14.2 Ethical committee review

Before the start of the study or implementation of any amendment we will obtain approval of the study protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and GP information letters if applicable from the REC. All correspondence with the REC and HRA will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

## 14.3 Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the REC and HRA.

The only circumstance in which an amendment may be initiated prior to HRA approval is where the change is necessary to eliminate apparent, immediate risks to the patients (Urgent Safety Measures). In this case, accrual of new patients will be halted until the REC approval has been obtained.

## 14.4 Peer Review

This study has been peer reviewed by the National Institute for Health Research. The Peer Review information can be forwarded on request.

## 14.5 Declaration of Helsinki and Good Clinical Practice

The study will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

### 14.6 GCP Training

All study staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this study. This training should be updated every 2 years or in accordance with Trust's policy.

## 15 Sponsorship, Financial and Insurance

Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge are jointly sponsoring the study. The study is funded by National Institute for Health Research as part of a Research for Patient Benefit project grant (Reference NIHR200495).

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical study caused through the negligence of its employees and honorary contract holders. The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising thorough participation in the clinical trial.

As all studies will occur either at the time of pre-existing clinical visits, or will be undertaken at home, no finances are available for patient expenses or travel costs.

## 16 Protocol Compliance and Breaches of GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action.

## 17 Publications policy

Ownership of the data arising from this study resides with the study team. On completion of the study the data will be analysed and tabulated and a Final Study Report prepared.

The Study Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of contributors and if there are named authors, these should include the study's Chief Investigator(s), Statistician(s) and Study Manager(s). If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least.

All publications will acknowledge that their research has been supported wholly or in part by NIHR using the format, "This report is independent research funded by the National Institute for Health Research (Research for Patient Benefit, Social Cognition Assessment and Rehabilitation for Families living with Brain Tumour (SCARF-BT) : a Feasibility Study, NIHR200495). The views expressed in this publication are those of the author(s) and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care."
The results of the study will be made available to participants on request from their PI after the Final Study Report and after papers have been published. Patients/families will

be invited to a dissemination event held in Cambridge to get their input into the interpretation of these results.

## 18 References

1. Burnet NG, Jefferies SJ, Benson RJ, Hunt DP, Treasure FP. Years of life lost (YLL) from cancer is an important measure of population burden--and should be considered when allocating research funds. *Br J Cancer* 2005; **92**(2): 241-5.

2. Kurian KM, Jenkinson MD, Brennan PM, et al. Brain tumor research in the United Kingdom: current perspective and future challenges. A strategy document from the NCRI Brain Tumor CSG. *Neuro-Oncology Practice* 2018; **5**(1): 10-7.

3. Driscoll DM, Dal Monte O, Grafman J. A need for improved training interventions for the remediation of impairments in social functioning following brain injury. *J Neurotrauma* 2011; **28**(2): 319-26.

4. Babbage DR, Yim J, Zupan B, Neumann D, Tomita MR, Willer B. Meta-analysis of facial affect recognition difficulties after traumatic brain injury. *Neuropsychology* 2011; **25**(3): 277-85.

5. Radice-Neumann D, Zupan B, Babbage DR, Willer B. Overview of impaired facial affect recognition in persons with traumatic brain injury. *Brain Inj* 2007; **21**(8): 807-16.

6. Bornhofen C, McDonald S. Emotion perception deficits following traumatic brain injury: a review of the evidence and rationale for intervention. *J Int Neuropsychol Soc* 2008; **14**(4): 511-25.

7. Zupan B, Neumann D, Babbage DR, Willer B. The importance of vocal affect to bimodal processing of emotion: implications for individuals with traumatic brain injury. *J Commun Disord* 2009; **42**(1): 1-17.

8. McDonald S, Flanagan S. Social perception deficits after traumatic brain injury: interaction between emotion recognition, mentalizing ability, and social communication. *Neuropsychology* 2004; **18**(3): 572-9.

9. Spikman JM, Milders MV, Visser-Keizer AC, Westerhof-Evers HJ, Herben-Dekker M, van der Naalt J. Deficits in facial emotion recognition indicate behavioral changes and impaired self-awareness after moderate to severe traumatic brain injury. *PLoS One* 2013; **8**(6): e65581.

10. Zupan B, Neumann D. Affect recognition in traumatic brain injury: responses to unimodal and multimodal media. *J Head Trauma Rehabil* 2014; **29**(4): E1-E12.

11. Cacioppo S, Capitanio JP, Cacioppo JT. Toward a neurology of loneliness. *Psychol Bull* 2014; **140**(6): 1464-504.

12. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. *The New England Journal of Medicine* 2005; **352**(10): 987-96.

13. Sage W, Fernandez-Mendez R, Crofton A, et al. Defining unmet clinical need across the pathway of brain tumour care – a patient and carer perspective. *Cancer management and research* 2019; **11**: 2189-202.

14. Campanella F, Fabbro F, Ius T, Shallice T, Skrap M. Acute effects of surgery on emotion and personality of brain tumor patients: surgery impact, histological aspects, and recovery. *Neuro Oncol* 2015.

15. Khan F, Amatya B, Ng L, Drummond K, Galea M. Multidisciplinary rehabilitation after primary brain tumour treatment. *Cochrane Database of Systematic Reviews* 2015.

16. Khan F, Amatya B, Drummond K, Galea M. Effectiveness of integrated multidisciplinary rehabilitation in primary brain cancer survivors in an Australian community cohort: a controlled clinical trial. *Journal of rehabilitation medicine* 2014; **46**(8): 754-60.

17. Neumann D, Babbage DR, Zupan B, Willer B. A randomized controlled trial of emotion recognition training after traumatic brain injury. *J Head Trauma Rehabil* 2015; **30**(3): E12-23.

18. Hirst A, Philippou Y, Blazeby J, et al. No Surgical Innovation Without Evaluation: Evolution and Further Development of the IDEAL Framework and Recommendations. *Ann Surg* 2018: [Epub ahead of print Apr 24 2018].

19. Fernández-Méndez R, Rastall RJ, Sage WA, et al. Quality improvement of neuro-oncology services: integrating the routine collection of patient-reported, health-related quality-of-life measures. *Neuro-Oncology Practice* 2018; **[Epub ahead of print] 17 October 2018**.

20. Nowicki S, Duke MP. Individual-differences in the non-verbal communication of affect-the diagnostic-analysis of nonverbal accuracy scale. *Journal of Nonverbal Behaviour* 1994; **18**(1): 9-35.

21. Guest G, Namey E, Taylor J, Eley N, McKenna K. Comparing focus groups and individual interviews: findings from a randomized study. *International Journal of Social Research Methodology* 2017; **20**(6): 693-708.

22. Guest G, Bunce A, Johnson L. How many interviews are enough?: An experiment with data saturation and variability. *Field Methods* 2006; **18**(1): 59-82.

23. Krueger RA, Casey MA. Focus Groups: a practical guide for applied research. 5th Ed. ed: Sage Publications, London; 2015.

24. Lincoln YS, Guba EG. Naturalistic inquiry: California: SAGE Publications; 1985.

25. Maringwa J, Quinten C, King M, et al. Minimal clinically meaningful differences for the EORTC QLQ-C30 and EORTC QLQ-BN20 scales in brain cancer patients. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2011; **22**(9): 2107-12.

26. Fielding S, Ogbuagu A, Sivasubramaniam S, MacLennan G, Ramsay CR. Reporting and dealing with missing quality of life data in RCTs: has the picture changed in the last decade? *Qual Life Res* 2016; **25**(12): 2977-83.

# 19 Appendices

## 19.1 Appendix 1 - Study Management / Responsibilities

*19.1.1 Patient registration*

Registration will be carried out by the participating site.

*19.1.2 CRF Completion & Data management*

Data will be collected on CRFs with participants' data, and should be entered on to the system within 28 days of a patient visit.

*19.1.3 Preparation & submission of amendments*

The SMG will be responsible for preparing and submitting amendments.

*19.1.4 Preparation and submission of Annual Safety Report/Annual Progress Reports*

The SMG and CI will be responsible for generating the Annual Progress Reports.

*19.1.5 Data protection/ confidentiality*

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.

The CRF will contain the patient's gender assigned at birth, age at registration and unique study registration number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. The study team will be undertaking activities requiring the transfer of patient NHS number.

This transfer of patient NHS number is disclosed in the Patient Information Sheet. The study team will preserve the confidentiality of participants taking part in the study.

*19.1.6 Study documentation & archiving*

The PI at each investigational site must make arrangements to store the essential study documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File until the sponsor informs the investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest).

In addition, the PI is responsible for archiving of all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from authorities). The PI is required to ensure the continued storage of the documents, even if the PI, for example, leaves the clinic/practice or retires before the end of required storage period.

Delegation must be documented in writing.

All CRFs will be archived onto an appropriate media for long-term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

## 19.2 Appendix 2 – WHO Performance Scale

| Score | Definition |
|---|---|
| 0 | Asymptomatic; fully active, able to carry on all pre-disease activities without restriction |
| 1 | Symptomatic; Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work) |
| 2 | Symptomatic; Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | Symptomatic; Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any self care. Totally confined to bed or chair. |
| 5 | Dead |