Caregiver and Patient less-Burden Life Evaluation Study - Phase II Observational study (CaPaBLE) Protocol

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Sponsor

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

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This protocol describes the CaPaBLE study 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 Frame Work 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.

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
CaGI	Caregiver Generated Index
CarGoQoL	CareGiver Oncology Quality of Life
CRF	Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
GBM	Glioblastoma
HGG	High Grade Glioma
HRQoL	Health-related Quality of Life
QoL	Quality of Life
MDT	Multi-Disciplinary Team
MoCA	Montreal Cognitive Assessment
PGI	Patient Generated Index
PIS	Patient Information Sheet
PPI	Patient and Public Involvement
PS	Performance Status
SAE	Serious Adverse Event

KEYWORDS
Health-related quality of life; brain tumours; caregiver; patient generated index; high grade glioma

STUDY SUMMARY

TITLE	Caregiver and Patient less-Burden Life Evaluation -Phase II Observational study (CaPaBLE Study)
DESIGN	Phase II non-randomised pragmatic cohort study of patients and caregivers
AIMS	Explore the feasibility and acceptability of novel, personalised measures of how an illness and its treatment can affect the areas of life most important to an individual with a brain tumour and their caregivers. Identify the similarities and differences in ratings of health-related quality of life between novel, personalised and standard measures in patients with brain tumours and their caregivers, over a period of 6 months Measure the statistical properties (correlation, variation and stability) of novel, personalised and standard measures over time
OUTCOME MEASURES	Feasibility and acceptability of novel, personalised measures of HRQoL in patients with brain tumours and their caregivers which will be measured as completion rates) Identify the similarities and differences in ratings of HRQoL between novel, personalised and standard measures in patients with brain tumours and their caregivers, over a period of 6 months Measure correlation, variation and stability between PGI/ CaGI and standard measures over time
POPULATION	Newly diagnosed/ recurrent high-grade primary brain tumour patients and their caregivers
ELIGIBILITY	Inclusion Criteria -Patient 1. Newly diagnosed, or recurrent, high-grade primary brain tumour. We define a high-grade tumour as any grade 3 or 4 primary brain tumour (including meningioma). 2. Newly diagnosed patients intending to undergo neurosurgical biopsy or resection, or to start a course of radical (>=45Gy) radiotherapy or a course of chemoradiotherapy or stereotactic radiotherapy. 3. Recurrent brain tumours patients undergoing further treatment including surgery, chemotherapy or re-irradiation. 4. Performance status 0, 1, or 2 5. Able to provide written informed consent. 6. Intention to attend at least 5 clinic visits over a six-month period to the study site 7. Age 18 years and above 8. Willing to undertake study-specific measures

	Inclusion Criteria -Caregiver 1. Main caregiver of patient with newly diagnosed or recurrent high-grade primary brain tumour. 2. Caregiver of patient receiving treatment (surgery and/or radiotherapy/ chemotherapy) expected to last >= 3 weeks in total 3. Aged 18 and above 4. Intention to attend at least 5 clinic visits over a six-month period to the study site. 5. Willing to undertake study-specific measures 6. Able to provide written informed consent
DURATION	Study will be open for 2 years; Participants will be on study for 6 months

1. INTRODUCTION

1.1 BACKGROUND

Despite some advances in treatment, the prognosis for patients with high grade brain tumours remains poor, and it is well recognised that both the disease and its treatment have the potential to affect the day to day lives of patients and their caregivers. However, the only tools currently available to get a formal understanding of quality of life are long questionnaires which do not allow for individuals to express their own opinions about what is important to their lifestyle. Moreover, "quality of life" is a difficult concept to define as its meaning may be different to different people. In addition, the nature of a patient's symptoms due to brain tumours, notably their degree of cognitive impairment, can be a barrier for questionnaire completion. For these reasons, the completion of HRQoL questionnaires, even within the context of a clinical trial, remains poor ((Taphoorn *et al.*, 2010; Wick *et al.*, 2016; Bitterlich and Vordermark, 2017).

Of note when discussing Quality of Life assessment is need to clarify the various terms used within the accompanying literature. Resulting from the diversity of intended uses, there are a variety of terms and associated assessment tools. Terms like "health status" are associated with a persons' disease state and physical performance, these are often clinician reported outcomes and include scales such as the ECOG Performance Scale and Adult Comorbidity Evaluation 27. "Quality of life" is seen as the most subjective term which is associated with an individuals' overall well-being and their view in comparison to expectations (own and societal); QoL questionnaires will include items on standard of living, social integration and personal relationships. "Health Related Quality of Life" is understood to be the impact on QoL in response to health state, this term can incorporate many domains and related questionnaires would include items covering self-care, pain and depression - these patient reported outcome tools most commonly used during clinical trials.

Currently the standard HRQoL questionnaire for brain tumour patients used in clinical trials is the EORTC QoL-Core30 (QLQ-C30) with an additional brain tumour module (BN20). In total these questionnaires come to 50 questions, though it is recognised that with the specific nature of brain tumour symptom presentation not all domains may be required for every patient. (Osoba *et al.*, 1996). Methods for item reduction have been trialled through the use of Computerised Adaptive Testing (CAT) however this is a complex process necessitating software implementation (Dirven *et al.*, 2017). Furthermore, the development and validation process for HRQoL questionnaires inherently makes them slow to respond to changes in available clinical treatments. As discussed in the work of the RANO PRO initiative (Dirven *et al.*, 2018), changes to side effect profiles mean that questionnaires developed 10 or more years ago no longer encompass issues of relevance to patients on current treatments.

For caregivers, a diagnosis of a brain tumour can result in negative outcomes for their own quality of life by impacting on areas like finances, free time and their own health needs. These have led to caregiver QoL assessment being included in research priorities set by national think tanks including the James Lind Alliance, as well as being highlighted within our own patient and public involvement feedback sessions. One of the most recent caregiver specific QoL tool is the CareGiver Oncology

Quality of Life (CarGOQoL) questionnaire. This is a validated tool for use with partners, parents and children. Its 29 items cover 10 domains (psychological well-being, burden, relationship with healthcare, administration and finances, coping, physical well-being, self-esteem, leisure time, social support and private life) (M. *et al.*, 2007, 2018; Brown *et al.*, 2008; Munoz *et al.*, 2008; Whalen and Buchholz, 2009; Flores *et al.*, 2014; Piil *et al.*, 2015; Baumstarck *et al.*, 2018; Reblin *et al.*, 2018).

One approach to reducing questionnaire burden is to use a process known as patient generated index (PGI) (Ruta *et al.*, 1994). In contrast to traditional QoL questionnaires which have defined domains to complete, the PGI allows individuals to suggest areas of their own lifestyle they consider to be important and provides a method for rating their significance. The process of using PGI has been successfully used with cancer patients, these studies have also highlighted the brain tumour patient group as potentially benefitting from the application of this tool in light of the specific symptoms each patient may present with. Methods similar to the PGI have been used with caregivers, though most commonly in the paediatric and dementia care settings where the opinions raised are as a proxy measure for patient QoL (Hogan *et al.*, 2013; Tang *et al.*, 2014; Aburub *et al.*, 2016a; H. *et al.*, 2016).

1.2 RATIONALE FOR CURRENT STUDY

Outside of clinical trials, the use of repeat QoL measurement for brain tumour patients and their caregivers in regular oncology follow up is poor. This is largely due to the same factors which limit completion rates of standard QoL questionnaires during trials, notably the lengthy questionnaire formats and complication of neurological deficit following disease and treatment.

Currently, QoL concerns are routinely recorded using the Holistic Needs Assessment. However, the outcome of this tool does not include a numerical QoL outcome and cannot easily track changes over time. In routine practice, this is also not used with caregivers.

To try to facilitate higher QoL completion rates with more personalised outputs, the CaPaBLE study intends to assess the feasibility of using the PGI process with patients diagnosed with brain tumours. Additionally, we will use the same tool to assess QoL of their main caregiver - a novel method we are terming the Caregiver Generated Index (CaGI). The results of PGI and CaGI will be compared to existing standard QoL questionnaires to get an understanding how well they capture the impact of living with this new diagnosis.

Our intention is that, if proved feasible, the use of PGI and CaGI in routine practice would deliver longitudinal patient QoL data which would help identify areas of need and direct the use of suitable services.

2. STUDY OBJECTIVES

2.1 AIMS

1. Explore the feasibility and acceptability of novel, personalised measures of HRQoL in patients with brain tumours and their caregivers.
2. Identify the similarities and differences in ratings of health-related quality of life between personalised and standard measures in patients with brain tumours and their caregivers, over a period of 6 months
3. Measure correlation, variation and stability of novel personalised measures and standard measures over time

2.2 OBJECTIVES

1. To explore the feasibility and acceptability of using PGI/ CaGI to assess HRQoL over time in patients with high-grade glioma (HGG) and their caregivers
2. To assess how changes in HRQoL as measured through standard approaches and personalised subsets + PGI/ CaGI relate to one another
3. To assess the impact of high grade, malignant primary brain tumours on quality of life in newly diagnosed patients and track changes in reported QoL throughout treatment and disease progression
4. To assess the impact on quality of life of being a caregiver for a patient with newly diagnosed, high grade, malignant primary brain tumours and track changes in reported caregiver QoL throughout treatment and disease progression
5. To identify differences and relationships between QoL scores expressed by patients and caregivers over time
6. To assess patient, caregiver and professional views on the comparative benefits and drawbacks of standard approaches and PGI/ CaGI

3. STUDY DESIGN

CaPaBLE is a prospective, observational, phase 2 non-randomised pragmatic cohort study of patients and caregivers, from diagnosis to six months.

All baseline assessments will be carried out at the local site as these will normally be done at the time of consent. Once consent has been taken in person, the option of video or telephone consultations will be considered on a patient/ caregiver basis by the treating clinical team. This is an already established service provided by the Neuro-oncology team at Imperial NHS Trust for those that are unable to attend the appointment in person.

3.1 SAMPLE SIZE

The target sample size for this observation, longitudinal study is 130 (80 patients and 50 caregivers), using a 20% patient and caregiver dropout rate. Our study design is based on a close reading of previous studies. Based on previous work, we estimated that a sample size of 80 patients is needed to allow for an analytical sample of 60. We expect that not all caregivers will participate, and thus we allow for a differential recruitment.

3.2 PARTICIPANTS

The target population of this study is patients with newly diagnosed (pre first treatment) or recurrent high-grade primary brain tumour and their caregivers. To best reflect clinical practice, we define a high-grade tumour as any grade 3 or 4 primary brain tumour (including meningioma). We will enrol participants from the joint Neuro-Oncology clinic, as early as possible in their diagnostic pathway. We will enrol those with brain tumours who have recently been diagnosed and are about to start a course of treatment or those diagnosed with recurrent disease and undergoing a second line treatment.

People who take on the caregiver role do not identify always themselves as caregiver therefore, for the purpose of this study we will use Macmillan's definition of a caregiver - 'Someone who, unpaid, looks after a person with cancer who couldn't manage without this help'. In practice we would also include any person identified by the patient as being essential for assisting in the management of their day-to-day and clinical needs.

3.3 ASSESSMENTS

Assessments for patients with high grade gliomas are as follows:

- Background information (gender, age, ethnicity etc)
- Full medical history (personal health history (any previously known health problems) and family health history (details about health problems that blood relatives have had during their lifetimes)
- Diagnosis
- Medications that you are currently on
- Physical examination guided by clinical consultation
- Performance status
- Any other know health conditions (ACE 27 Questionnaire)
- Recent imaging and blood tests performed for routine clinical practice
- A brief assessment of your memory and concentration which normally takes 5-10 minute (MoCA)

Assessments for caregivers are as follows

- Background information (gender, age, ethnicity etc)
-
- Performance status
- Any other know health conditions (ACE 27 Questionnaire)

3.4 QUESTIONNAIRES

Patients will be asked to complete the following questionnaires at certain study time points:

- PGI is a three-step process: Patients lists five areas most affected by illness and an initial box asks, “all other areas of your life affected by your cancer and treatment.” Patient rates each of the 6 areas on a scale 0 (worst imaginable) to 6 (very best imaginable); Patient distributes 10 points between the 6 areas with the most points going to the more important areas
- EORTC QLQ30 covers five functioning scales (physical, social, role, cognitive, and emotional functioning), eight symptom scales (fatigue, nausea/vomiting, pain, dyspnea, sleep disturbances, appetite loss, constipation, and diarrhea), financial impact, and overall quality of life, 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.
- 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 QLQ30 the raw scores are converted to a 0-100 scale and a higher score for this questionnaire represents a poorer QoL.
- EQ-5D-5L is a short, quick and cognitively undemanding assessment consisting of 5 questions and a Visual Analog Scale. It has been used in a wide range of health conditions and treatments and therefore makes it an ideal tool for comparative assessment. Furthermore, the EQ-5D-5L can then be adapted to a single index value.
- ACE 27 Questionnaire, taken at enrolment only by a member of the research study team. To assess background health status of patient.

Caregivers will be asked to complete the following questionnaires at certain study time points

- CaGI which will be based on the same concept as the PGI - three-step process: Caregiver lists five areas most affected by illness and an initial box asks, “all other areas of your life affected by your loved one’s cancer and treatment.” Caregiver rates each of the 6 areas on a scale 0 (worst imaginable) to 6 (very best imaginable); Caregiver distributes 10 points between the 6 areas with the most points going to the more important areas
- CareGiver Oncology Quality of Life (CarGOQOL) questionnaire. A validated tool for use with partners, parents and children of oncology patients contains 29 items covering 10 domains (psychological well-being, burden, relationship with healthcare, administration and finances, coping, physical well-being, self-esteem, leisure time, social support and private life)
- EQ-5D-5L is a short, quick and cognitively undemanding assessment consisting of 5 questions and a Visual Analog Scale. It has been used in a wide range of health conditions and treatments and therefore makes it an ideal tool for comparative

assessment. Furthermore the EQ-5D-5L can then be adapted to a single index value.

- ACE 27 Questionnaire, taken at enrolment only by a member of the research study team. To assess background health status of caregivers.

3.5 RECRUITMENT PROCESS

Participants will be recruited from three tertiary care centres (Imperial College Healthcare NHS Trust, Barts Health NHS Trust and Guys & St Thomas NHS Foundation Trust).
Potential participants will include any patient that is referred to the Brain Tumour MDT and/or neuro-oncology clinic with a suspected new, or recurrent, high grade brain tumour and plan is for:

- neurosurgical biopsy or resection,
- start a course of radical radiotherapy (≥45 Gy)
- course of chemoradiotherapy
- stereotactic radiotherapy
- or for re-treat for relapsed disease.

As clinically indicated, patients will come to their clinic appointment, normally with a caregiver, to discuss treatment options. At this point, the treating doctor/ JT/ LS/ member of the study team will provide patient and caregiver with a written patient information sheet (PIS) to read. Both the caregiver and patient should be given sufficient time to consider whether or not they would like to participate in the study. If the patient and caregiver feel that they have a full understanding of the research and what it entails and have had the opportunity to ask any questions they may have, a member of the study team will consent them onto the study and complete the baseline Case Report Form (CRF).

Participants will be divided into three cohorts for eligibility/ recruitment into the study:

1. Patient and caregiver both consent for study
2. Patient consents for study and the caregiver does not consent to take part in study
3. Patient does not consent to being part of study but gives consent for research team to have access to medical records. Caregiver consents to being enrolled into study.

Participants will then take part in an observational, longitudinal study of HRQoL from diagnosis to six months. The assessment process will be as follows:

1. Screening of patients from Brain MDT and Neuro-Oncology clinics
2. Patient comes to clinic (as clinically indicated) with caregiver

3. Caregivers will be approached to take part in the study if they attend one of the initial outpatient appointments with the patient participant and will be given a separate participant information sheet (PIS) and consent form to sign.
4. Patient/ caregiver given PIS to read. If patient/ caregiver feels that they have a full understanding of the research and what it entails, they will be given the consent form to sign to provide informed consent
5. Patient/ caregiver enrolment into the study
6. Explanation of how PGI/ CaGI will be completed at each time visit
7. Baseline assessments to be completed (see trial schema in assessment and follow up)
8. At each visit, patient/ caregiver completes the PGI/CaGI first followed by standard HRQoL measures
9. Patients and caregivers will be given the opportunity to complete assessments online where study sites (i.e. Hospital Trusts) are already using secure online portals for patient care as these are an acceptable method of gathering patient data. These portals will only be used if they already have approval from the trust and are used as part of routine clinical care. We are keen to include the use of such methods, as otherwise we run the risk of forcing a backward step (i.e. taking sites that use a portal and then forcing them back to paper-based data collection).
10. Assessments will be done at baseline, 6 weeks, 3,4 and 6 months (see trial schema in assessment and follow up)- we will assess at an individual participant level the best way to complete assessments e.g. on paper or using online mechanisms
11. With ongoing consent, patients and caregivers will be followed from enrolment for 6 months or to discontinuation of treatment or death. If a participating patient is discontinued from active treatment, they and their caregiver will be approached to continue with the research assessment timetable. In discussion, these future assessments could be completed remotely (via telephone or video call) to prevent coming to the hospital.

3.6 CONSENT

If a person is happy to participate in the study, one of the study team will obtain informed consent and we will complete baseline assessments. We will make people aware that the study is voluntary and that they do not have to take part. The decision to take part will not affect their care or treatment, including their relations with the direct care team. Given the low risk nature of this study, and in line with our other observational studies, we will allow participants to give consent and enrol on the same day. However, we are also happy for people to be given the PIS and enrol later. Potential participants will be given the time to consider fully the implications of taking part in research and this may vary between people. Once people have had enough time to process and ask questions, should they have any, signed informed consent can be taken. The right of people to refuse to participate without giving reasons shall be respected.

If a patient does not want to take part in the study, and a Caregiver does, informed consent will be taken from the Caregiver to participate, and consent will be taken from the patient to gain access to the patient's medical record.

All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. If a patient 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.

3.7 DATA COLLECTION

For this study we will utilise a similar method as Hogan et al 2013 for undertaking the process of PGI and CaGI. We will provide a trigger list of sample areas/ concerns that are commonly raised in the literature on HRQoL in brain tumour patients and caregivers. Participants will be allowed to make use of one or more items from this list or generate their own.

As part of the study assessments, we will undertake audio recordings of the assessment sessions. These will be used to provide an unbiased record of the research process and may be used for further research in the future.

3.8 STUDY OUTCOME MEASURES

Primary Outcome measures

1. Feasibility and acceptability of novel, personalised measures of HRQoL in patients with brain tumours and their caregivers, which will be assessed using completion rates.

2. Similarities and differences in ratings of HRQoL between novel, personalised and standard measures in patients with brain tumours and their caregivers, over a period of 6 months

3. Correlation, variation and stability between PGI/ CaGI and standard measures over time; in relation to treatment, disease progression and cognitive function

Secondary Outcome measures

1. Patterns of response to PGI/ CaGI and changes in impact on quality of life for both caregivers and patients with brain tumours

2. Correlation and divergence over time between QoL scores expressed by patients and caregivers

3. Patient, caregiver and professional views on the comparative benefits and drawbacks of standard approaches and PGI/ CaGI

4. PARTICIPANT ENTRY

4.1 INCLUSION CRITERIA

Inclusion Criteria -Patient

1. Newly diagnosed, or recurrent, high-grade primary brain tumour. We define a high-grade tumour as any grade 3 or 4 primary brain tumour (including meningioma).
2. Newly diagnosed patients intending to undergo neurosurgical biopsy or resection, or to start a course of radical (≥45Gy) radiotherapy or a course of chemoradiotherapy or stereotactic radiotherapy.
3. Recurrent brain tumours patients undergoing further treatment including surgery, chemotherapy or re-irradiation.
4. Performance status 0, 1, or 2
5. Able to provide written informed consent.
6. Intention to attend at least 5 clinic visits over a six-month period to the study site
7. Age 18 years and above
8. Willing to undertake study-specific measures

Inclusion Criteria -Caregiver

1. Main caregiver of patient with newly diagnosed or recurrent high-grade primary brain tumour.
2. Caregiver of patient receiving treatment (surgery and/or radiotherapy/ chemotherapy) expected to last ≥ 3 weeks in total
3. Aged 18 and above
4. Intention to attend at least 5 clinic visits over a six-month period to the study site.
5. Willing to undertake study-specific measures
6. Able to provide written informed consent

4.2 EXCLUSION CRITERIA

Exclusion Criteria -Patient

1. Diagnosed with a low-grade brain tumour (including grade 1 and 2 meningiomas)
2. Poor performance status (PS 3,4) or rapidly deteriorating fitness and for best supportive care and/or symptom control only.
3. Diagnosed with a high-grade brain tumour but not planned for any intervention.
4. Language barriers
5. Poor cognition status based on clinical assessment/ Montreal Cognitive Assessment (MoCA)/ MDT
6. Refusal to participate

Exclusion Criteria -Caregiver

1. Severe cognitive problems based on the doctor's opinion
2. Language barrier

3. Ongoing active treatment for own medical condition expected to significantly limit attendance for study assessments (missing 2 or more clinic visits). To be assessed by attending clinical or research team.

4.3 WITHDRAWAL CRITERIA

The right of the participant to refuse to participate without giving reasons shall be respected. After the participant has entered the study the clinician will remain 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 shall 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. If a patient 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.

5. ASSESSMENT AND FOLLOW-UP

Patients will undergo standard follow up procedures (both clinical and imaging assessment) as part of their routine clinical care (monthly if on chemo-radiotherapy and 3-6 monthly during the follow up), and for this study will be followed from enrolment until 6 months. We intend to complete both patient and caregiver assessments at the same clinic visits. At all visits, the PGI/CaGI will be completed prior to any other assessment (EORTC QLQ30, BN20, CarGOQoL and EQ-5D-5L). At each visit the PGI/CaGI is completed anew, this will allow assessment of change in domains highlighted and the weighting ascribed to them.

To assess their previous medical history and concurrent medical conditions, the attending medical professional or researcher will complete the Adult Co-Morbidity Evaluation 27 with the caregiver at enrolment.

Patients and caregivers will be free to withdraw from the study at any time.

For validation purposes, on three visits patients and caregivers will be required to complete an additional assessment, EQ-5D-5L. This is a short, quick and cognitively undemanding assessment consisting of 5 questions and a Visual Analogue Scale. It has been used in a wide range of health conditions and treatments and therefore makes it an ideal tool for comparative assessment. Furthermore, the EQ-5D-5L can then be adapted to a single index value.

The end of the study is at the end of 6 months of follow up, discontinuation of treatment or death

		Enrolment/ Baseline	Week 2	Week 6	Month 3	Month 4	Month 6	Unexpected Visit
Patient	Demographic information	+						
	Medical history	+						
	Adult Co-Morbidity Evaluation 27	+						
	Diagnosis	+						
	MOCA assessment	+			+		+	
	EQ-5D-5L	+			+		+	
	Clinical information, Medication and imaging results	+	+	+	+	+	+	+
	ECOG PS	+	+	+	+	+	+	+
	Recent hospitalization	+	+	+	+	+	+	+
	PGI	+	+	+	+	+	+	+
	EORTC QLQ C30 & BN20	+	+	+	+	+	+	+
		Enrolment/ Baseline	**Week 2**	**Week 6**	**Month 3**	**Month 4**	**Month 6**	**Unexpected Visit**
Caregiver	Demographic information	+						
	Adult Co-Morbidity Evaluation 27	+						
	EQ-5D-5L	+			+		+	
	ECOG PS	+	+	+	+	+	+	+
	CaGI	+	+	+	+	+	+	+
	CarGOQoL	+	+	+	+	+	+	+

6. ADVERSE EVENTS

It is not anticipated that any adverse events will occur due to the nature of the study which consists of assessment, questionnaire and focus group which do not involve clinical invasive procedures. However, any questions concerning adverse events reporting will be directed to the Chief Investigator, and the sponsor

7. PATIENT AND PUBLIC INVOLVEMENT

The protocol has been reviewed by two patients and two caregivers (have experienced treatment for primary brain tumours). We will also include a patient and caregiver as part of the study management group to give their opinion on the design, management, discussion and dissemination of the study. These individuals will not be enrolled as participants in the study.

8. STATISTICS AND DATA ANALYSIS

The CI, Lillie Shahabi, and Co-investigator, James Tallant, will deal with the day to day management of the study and will ensure data completion and will help collate and check the data.

We will apply for the study to be NCRN-badged therefore if successful the local NCRN research nurses will be able to provide recruitment support. At Imperial College Health Care Trust, data will be collected in clinic on iPads, on Care Information Exchange (CIE – secure online platform currently available at ICHT) or on paper by the dedicated study team and stored directly onto ICHT Trust computers. At the other centres data will be collected in clinic using iPads/paper by the site-specific study team and stored on local secure NHS computers. At the end of each month data collected will be transferred to the main ICHT computer in a pseudonymised format for analysis.

8.1 STUDY DESIGN AND SAMPLE SIZE

Our study design is based on a close reading of previous studies, and our target sample size is 130 patients and caregivers. Based on previous work, we estimated that a sample size of 80 patients is needed to allow for an analytical sample of 60 (Hogan *et al.*, 2013; Tang *et al.*, 2014; Aburub *et al.*, 2016b). We expect that not all caregivers will participate, and thus we allow for a differential recruitment of 50 caregivers. Previous work exploring the use of PGI has typically enrolled 30 - 80 patients. Our work should place us towards the top end of this range.

Formal statistical planning is difficult without knowing rates of completion and drop-out. However, if we want to estimate the concordance (as agreement between standard QoL measures and PGI) using Spearman's rank correlation coefficient, then there is a formula to calculate these confidence intervals. If we assume that the true correlation coefficient is ~0.5 (in line with previous work in 55 patients with traumatic brain injury and 192 patients with a range of cancers) then if we find an r =

0.5 and analytical n = 60 the 95% confidence intervals for the r value are 0.28 - 0.67. In the caregiver cohort, if calculated r = 0.5 and n = 30 then the 95% confidence intervals on r is 0.17 - 0.73.

We accept that these 95% confidence intervals are large (although in line with the literature) which is why this is a feasibility and pilot study.

The main aim of CaPaBLE is to demonstrate feasibility and acceptability of using the PGI and CaGI in patients with brain tumours and caregivers. We will assess face and content validity of the PGI by assessing areas of patients' lives affected by the cancer and the treatment and comparing those to domains in the standard measures.

8.2 VALIDITY

We will assess face and content validity of the PGI by assessing areas of patients' lives affected by the cancer and the treatment and comparing those to domains in the standard measures. Overall the standard measures for patients capture 36 symptomatic and functional domains: 25 covered by the EORTC QLQ-C30 and a further 11 covered by the brain tumour module (BN20); for the caregivers the standard measure CarGoLQoL covers 10 domains. We will measure how many of these are covered by the PGI, and whether multiple PGI concerns lie within one domain, and whether PGI concerns lie outside the domains. We will represent this by reporting number and proportion of domains covered and number of a proportion of PGI concerns that were not captured in the standard measures. We will represent coverage with spider-web plots.

We will assess construct validity by assessing correlation between normalised standard measure scores and PGI scores. In line with previous work, we will also use Bland-Altman plots to assess this relationship.

8.3 RESPONSIVENESS

We will assess responsiveness by examining correlations between normalised changes from baseline. However, this is subject to some statistical biases, and so we will attempt to model change, using baseline HRQoL values as a baseline variable. We will consider the use of repeated-measures ANOVA (RM-ANOVA). We will compare QLQ C30, PGI and EQ5D5L (patients) CarGoQoL, CaGI, EQ5D-5L as pairwise comparisons (3 comparisons for both patients and caregivers). We will also assess relationship between QLC C30 and CarGOQoL and CaGI and PGI (4 comparisons) and EQ5D-5L (1 comparison). We will account for within-patient clustering of scores in our analyses and examine the role of centre as a variable in determining HRQoL scores.

We will use stepwise backwards multiple regression to model the relationship between PGI and QLQ C30 and PGI and E5QD-5L and CaGI and CarGoQoL and CaGI and EQ5D-5L. We consider the use of splines for fitting non-linear responses.

We will examine patients who are under 40 and PS 0/1 vs. patients over 60 and PS 2+ and assess their QoL. We would expect the QoL in the latter group to be worse, and we will use this as a simple validation of conventional QoL measures and personalised novel measures.

8.4 AUDIO-RECORDING

For the purpose of this study, we will capture audio recording to ensure we have an unbiased record of the consultation. These recordings may be used for further research.

8.5 DATA GOVERNANCE

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 HRQoL. We will seek explicit consent to store the enrolment log, consent form and coded data for 10 years following completion of the study.

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.

9. REGULATORY ISSUES

9.1 ETHICS APPROVAL

The Chief Investigator has obtained approval from the HRA and Research Ethics Committee. The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study. 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.

9.2 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. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment. In these cases, we will use data up until this point.

9.3 CONFIDENTIALITY

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

9.4 INDEMNITY

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

9.5 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.

9.6 FUNDING

Imperial NIHR BRC: Imperial Health Care Charity ($64,951.14), and RM Partners ($60,003.00) are funding this study.

9.7 AUDITS

The study may 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 Frame Work for Health and Social Care Research

10. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Lillie Shahabi (CI), and James Tallant (co-I), and will ensure data completion and will help collate and check the data.

11. PUBLICATION POLICY

We will publish and disseminate the results and 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.

12. REFERENCES

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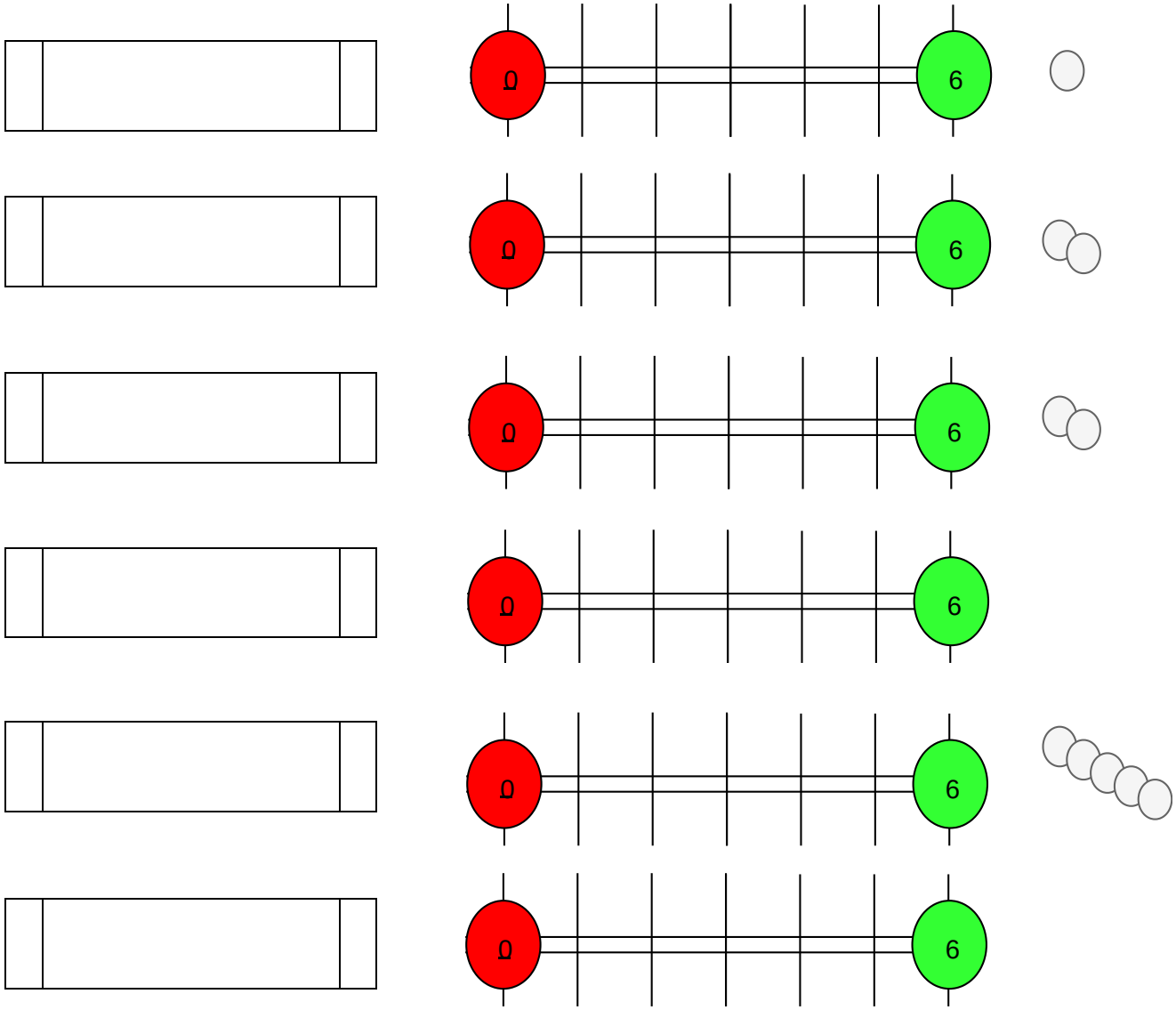
13. APPENDIX

13.1 APPENDIX 1 - PGI



13.2 APPENDIX 2 – EORTC- QLQ30

13.3 APPENDIX 3 – EORTC- BN20

13.4 APPENDIX 4 – EQ-5D-5L

13.5 APPENDIX 5 – CarGoLQoL

13.6 APPENDIX 6 – PIS/ CIS/ PIS (caregiver enrolment)

CaPaBLE PIS v1.5IRAS ID266261.pd

CaPaBLE PIS (Caregiver only) v1.5I

CaPaBLE CIS v1.5IRAS ID266261.pd