BT-LIFE

Brain **T**umours, **L**ifestyle **I**nterventions, and **F**atigue **E**valuation: a multi-centre, feasibility, Randomised Controlled Trial

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
CaCTUS	Cancer Clinical Trials Unit, Scotland
CI	Chief Investigator
CRF	Case Report Form
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
MREC	Main Research Ethics Committee
SAE	Serious Adverse Event
SCTRU	Scottish Clinical Trials Research Unit
SDV	Source Data Verification
TMG	Trial Management Group
TSC	Trial Steering Committee

TRIAL SUMMARY

Protocol ID	BT-LIFE
Protocol Title	Brain Tumours, Lifestyle Interventions and Fatigue Evaluation: a multi-centre, feasibility, Randomised Controlled Trial.
Development Phase	Feasibility Randomised Controlled Trial
Study Aims	In fatigued adult outpatients with a primary brain tumour, and in the setting of a multi-centre randomised controlled trial: 1) Assess the feasibility of delivering a structured lifestyle intervention (Health Coaching) and behavioural intervention (Patient Activation); 2) Determine their acceptability to patients and manageability for professionals; 3) Develop systems and pilot outcome measures for definitive RCTs of these interventions.
Primary Outcome	The feasibility of delivering Health Coaching and Patient Activation to fatigued patients with a primary brain tumour. Feasibility will be assessed by meeting a priori defined standards for recruitment and retention as follows: • recruitment will be feasible if 20 fatigued brain tumour patients can be recruited per centre over 12 months; • retention will be feasible if total attrition at T2 (endpoint) is less than or equal to 40%.
Secondary Outcomes	1) The acceptability of the interventions to patients. 2) The manageability of the interventions for professionals. 3) The development of systems and piloting outcome measures for future definitive RCTs of the interventions for fatigued brain tumour patients, including determination of mean change in outcome scale scores in each arm.
Study Design	Multi-centre, feasibility Randomised Controlled Trial with 16 weeks follow-up.
Patient Accrual	Eligible patients will be randomised to one of three study arms: control (n=20); Health Coaching (n=20); Health Coaching plus Patient Activation intervention (n=20)
Analysis	Will be performed when all patients have completed their assessments at the end of the 16 week follow up and all data has been cleaned and database finalised.

1. INTRODUCTION

1.1 Background & Trial Rationale

Each year, more than 10,000 adults in the UK are diagnosed with a primary brain tumour.[1] Many or most of them experience fatigue, as evidenced by consistent reports of fatigue prevalence of between 40-70%.[2,3] In turn up to forty percent[4] of these fatigued brain tumour patients regard it as 'severe', which strongly and independently reduces multiple domains of quality of life.[5,6] Fatigue is in other words, a problem both of high frequency and of high impact for people living with a brain tumour. The causes of fatigue are however multi-factorial and vary between individuals.[7] As a result complex interventions such as structured lifestyle or behavioural interventions have been proposed as treatment for fatigue.[8] These non drug-based treatments focus on changing aspects of the patient's lifestyle or behaviour. They have shown some efficacy in treating fatigue in patients with cancer arising out-with the central nervous system (CNS).[9,10]

It is therefore plausible that structured lifestyle and behavioural interventions could be effective treatments for fatigue in patients with a brain tumour. However two problems with this hypothesis must be addressed. The first is that the conclusions of prior studies may not apply to patients with a brain tumour because these studies have largely recruited patients with cancer arising out-with the CNS. Brain tumours by contrast inhabit a privileged location and may directly alter cognition, physical function, personality, and/or seizure threshold. These relatively 'brain-tumour specific' co-morbidities could subvert strategies known to be effective in other cancer patient groups. The natural solution to this problem is to study how to treat fatigue in patients with brain tumours specifically.

The second problem is that most prior studies included patients with little or no fatigue at baseline. They cannot therefore directly answer the clinically relevant question, which is how best to treat individuals with clinically significant fatigue.[8] Here the natural solution is to recruit and study patients with clinically significant fatigue. The few studies to do so suggest that complex interventions can be delivered effectively in fatigued patients.[11,12] But specifically which structured lifestyle and behavioural interventions could be studied?

<u>A structured lifestyle intervention: Health Coaching</u>
Health Coaching is a lifestyle intervention which targets basic elements of diet, exercise, sleep and stress. It has been developed and delivered in the community for several years by our collaborator.[13] Participants monitor their dietary intake, movement, rest and stress levels daily and in a structured way. Working in partnership with the Health Coach - an appropriately trained and qualified practitioner such as a personal trainer or physiotherapist - patients are supported to make incremental positive changes to their lifestyle. Because similar lifestyle interventions have been shown to be effective in treating fatigue in other cancer populations[10,14], we hypothesise that Health Coaching may be a effective treatment for fatigue in brain tumour patients.

<u>A structured behavioural intervention: Patient Activation</u>
Patient Activation (PA)[15] is a behavioural intervention which leverages the individual's knowledge and confidence so that they are 'activated' to self-manage their condition. Importantly, PA captures not only the patient's *beliefs* about their ability to self-manage but also the *likelihood* that they will put these beliefs into action. Empowering patients through the framework of PA is thought to improve autonomy, quality of life, patient satisfaction, and cost-effectiveness.[16] We hypothesise that Patient Activation could empower fatigued brain tumour patients to make and maintain lifestyle changes suggested by a Health Coach, potentially improving fatigue more than Health Coaching alone.

We wished to determine the level of existing evidence for these or similar lifestyle and behavioural interventions. To do this we systematically reviewed the evidence for effective interventions for fatigue in patients with a brain tumour.[17] We found that nearly all eligible RCTs examined psychostimulant drug treatments, such as methylphenidate or modafinil [(e.g.)18-20] We found limited evidence that cognitive rehabilitation may improve mental fatigue as a secondary consequence of treating cognitive impairment.[21,22] However, we found no high-quality studies of *any* non-pharmacological strategies such as lifestyle or behavioural interventions. Nearly all trials were further compromised by extending eligibility to non-fatigued patients. We concluded that there was a <u>clear need for studies that evaluate</u>

structured lifestyle and behavioural interventions for significant fatigue in people living with a brain tumour.

In this respect candidate studies would ideally meet some important criteria.

- They would ensure *clinical significance* by recruiting patients with high levels of fatigue at baseline.
- Given the limited state of current knowledge they would focus first and appropriately on studying the *feasibility* of delivering interventions in a Randomised Controlled Trial.
- They would show *novelty* by studying interventions previously unstudied in this population.
- They would *add value* by including a qualitative sub-study to understand the acceptability of interventions, alongside their feasibility.
- *Credibility* would be assured by the involvement of an accredited Clinical Trials Unit.
- The *exit strategy* would be clear: the feasibility study would develop systems in sufficient centres to recruit plausibly to a definitive trial.
- Such studies would ideally be run by a *collaborative and expert team* with a track record in neuro-oncology symptoms research.

1.2 Strategic importance of this research

The strategic vision of this study is to move towards better treatment for brain tumour-related fatigue. Nearly two-thirds of brain tumour patients experience fatigue, with 40% reporting that it has affected them severely.[4] Fatigue is regarded as a 'top ten' clinical research priority in people with a brain or spinal cord tumour, by the UK James Lind Alliance (JLA) Priority Setting Partnership in Neuro-oncology.[23] More broadly by focusing on aspects of holistic assessment, lifestyle, late effects, and survivorship care, this study also reflects current thinking in the cancer field. Our approach aligns with the new Cancer Strategy in England, the Transforming Cancer After Treatment programme in Scotland, and the National Cancer Survivorship Initiative. This proposal directly targets a top priority of patients, charities, policymakers, and the wider research community.

2. TRIAL OBJECTIVES

2.1 Primary Outcome

The feasibility of delivering Health Coaching and Patient Activation to fatigued patients with a primary brain tumour.

Feasibility will be assessed by meeting a priori defined standards for recruitment and retention as follows:

- Recruitment will be feasible if 20 fatigued brain tumour patients can be recruited per centre over 12 months;
- Retention will be feasible if total attrition at T2 (endpoint) is less than or equal to 40%.

2.2 Secondary Outcome

1) The acceptability of the interventions to patients.
2) The manageability of the interventions for professionals.
3) The development of systems and piloting outcome measures for future definitive RCTs of the interventions for fatigued brain tumour patients, including determination of mean change in outcome scale scores in each arm.

2.3 Objectives and Key Deliverables

We will obtain ethical and centre-specific approval for the study; gain access to neuro-oncology adult outpatient clinics; recruit 60 fatigued brain tumour patients from three centres; appraise the feasibility of Health Coaching and Patient Activation in fatigued participants; pilot outcome measures of fatigue impairment, functional impact, and efficacy of self-management; pilot measures of the confounding variables of mood change and cognitive impairment; pilot health economic measures; and gain a

deeper understanding of which components of the interventions are acceptable to whom and why, including their impact on the patient's primary carer. By doing so we will increase patient enrolment into early-phase clinical trials, while laying the ground for a definitive trial of non-pharmacological interventions for fatigue in people living with a brain tumour.

3. TRIAL DESIGN

3.1 General Design

BT-LIFE is a multi-centre feasibility Randomised Controlled Trial, summarised schematically here (Figure 1). It is designed in line with guidance on developing complex interventions from the MRC[24].

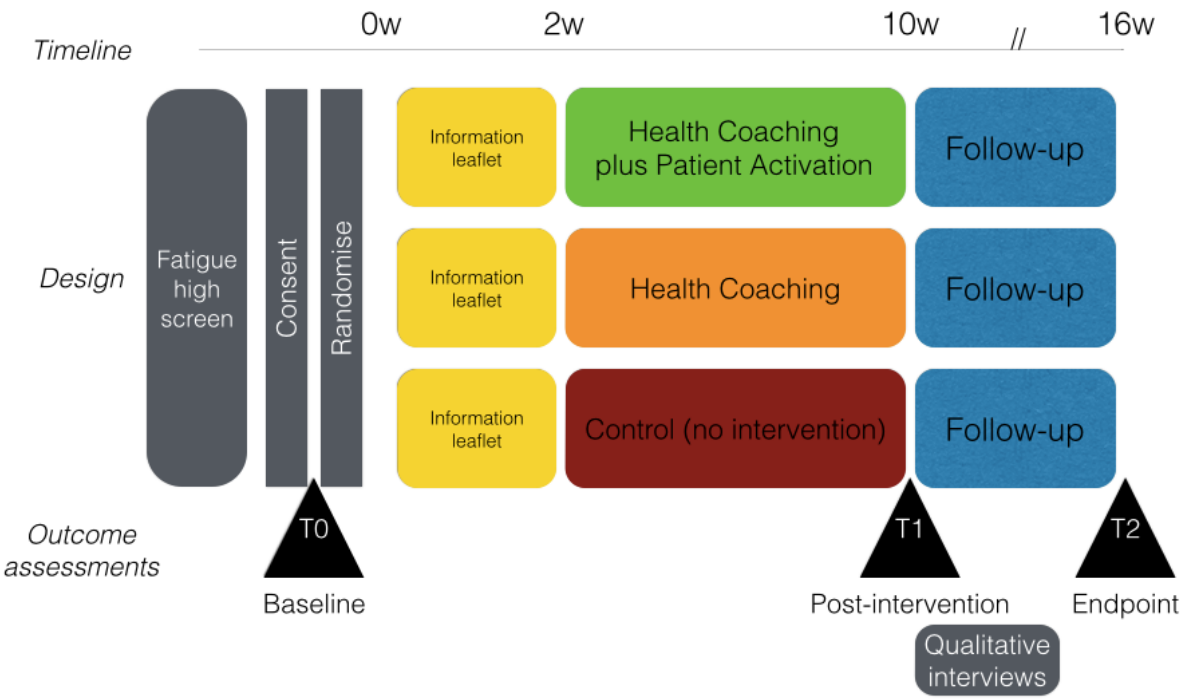

Figure 1: *Schematic overview of the Brain Tumours, Lifestyle Intervention and Fatigue Evaluation (BT-LIFE) multi-centre feasibility Randomised Controlled Trial.*

3.2 Inclusion Criteria

1. Patients aged 18 and above;
2. Diagnosed with any primary brain tumour;
3. >3 months post-completion of chemotherapy/radiotherapy;
4. Clinically and radiologically stable, as defined by no evidence of disease progression at most recent clinic appointment;
5. Moderate or severe fatigue (Brief Fatigue Inventory score ≥4/10, indicating at least 'moderate' severity of fatigue over the previous week) - criterion for Randomisation.

3.3 Exclusion Criteria

1. Radiological or clinical concern at most recent appointment over disease progression;
2. Significant cognitive impairment, dysphasia, or visual impairment limiting ability to complete questionnaires;
3. Patients unable to give informed consent, or who are unable or unwilling to comply with interventions.

3.4 Recruitment/Setting

Patients will be recruited from neuro-oncology outpatient clinics in three tertiary centres: Edinburgh, Glasgow, and Manchester. Patients due to attend clinic and who meet inclusion criteria 1-3 above will be identified ahead of time. The Patient Information Sheet (PIS) will be posted to them together with a covering letter from their usual treating clinician. In this manner patients will have sufficient time to consider information about the study.

Edinburgh site: the information letter will also include a brief fatigue screening questionnaire (Brief Fatigue Inventory, BFI). In the covering letter patients will be asked to complete the screening questionnaire and take it with them to clinic if they are interested in taking part. In clinic, patients who have brought the completed questionnaire (and who have moderate-severe fatigue) will be asked by a member of their usual clinical team if they are interested in taking part in the study.

Glasgow and Manchester sites: During the clinic appointment a member of the usual clinical team will enquire whether the patient may be interested in taking part in the study. If so, the usual team member will themselves administer the screening Brief Fatigue Inventory.

Patients who score ≥4/10 on the BFI will be eligible to continue in the full study. In all sites they will then be introduced to a Research Assistant or Research Nurse who will obtain informed consent from the patient
The Baseline Assessment (T0) will then be conducted. Follow-up Assessments (T1 and T2) will be arranged according to preference: either via further attendance at outpatient clinics, or by posting forms to participants to complete at home and return in a stamped addressed envelope.

Immediately after the Baseline Assessment, participants will be Randomised.

3.5 Randomisation Codes

After ensuring that the patient meets all the eligibility criteria and has consented to participate, the RA/RN will log onto www.sealedenvelope.com to randomise. An identification number will be issued which should be used in all correspondence. The RA/RN will notify SCTRU that a randomisation has occurred by emailing the randomisation confirmation securely to NSS.BT-Life@nhs.net. Participants will be randomised to one of three study arms:

- Control (n=20);
- Health Coaching (n=20);
- Health Coaching plus Patient Activation intervention (n=20).

These group sizes reflect national guidelines on appropriate group sizes for a feasibility study.[25]

Following randomisation, the participant's GP will be informed that they are taking part in the study.

It may be possible for participants to be recruited into other clinical trials, but this should be discussed with the CI, via SCTRU, before this is considered.

3.6 Withdrawal of Subjects

In recognition that fatigued participants may find Health Coaching tiring without wishing to withdraw from the study entirely, we will use a two-level framework for withdrawing consent.

Participants may partially withdraw consent at any point without having to give a reason (by withdrawing from active treatment in the study, for instance any participant who may find Health Coaching too onerous) and may continue to be followed up per protocol if they wish.

Participants may also fully withdraw consent at any point without having to give a reason. Data that has been gathered up to that point will be censored at the point of withdrawal, unless the participant wishes further that none of their data gathered at any time should be used, in which case it will be removed from study records.

Any participant who indicates to us that they wish to withdraw consent will be treated according to the "withdrawal of consent" flowchart (see supporting documents).

4. TREATMENT INTERVENTION

(Post-Randomisation):

Arm 1:

Control (n=20). Participants randomised to the control arm will continue to receive the highest possible standard of care and support from their neuro-oncology team, who will be informed that the patient has high fatigue. The participant will also receive high-quality written information on how to manage fatigue (see Fig 1 and supporting documents). They will then be followed up at T1 and T2.

Arm 2:

Health Coaching (n=20). Participants randomised to this arm will be treated as per Arm 1, but in addition will receive Health Coaching. They will be given an initial consultation form to complete. They will then receive a standardised first appointment with a trained Health Coach, in a clinical setting, by arrangement to suit. This initial face-to-face appointment will cover 1) consultation form review; 2) Measures (blood pressure, resting heart rate, height, weight); 3) Muscle Activation exercises 4) Review of guidance videos; 5) Goal setting until the next appointment. Participants will be given a fitbit-style monitor to wear for the duration of the study.

Participants will then record standardised information about their lifestyle, on paper using a custom-designed diary form. The following information (the 'DREEMS' approach) will be gathered as often as possible (max daily) with assistance from the patient's carer/relative if desired:

Drink.	Caffeine, alcohol, water (number of each kind of drink per day, self-report)
Rest.	Total sleep (hours per day, self-report)
Eating.	Various food groups (portions per day, self-report)
Exercise	Aiming 3x30 minute sessions per week (self-report)
Movement.	Total number of steps taken per day (objective recording byfitbit-style monitor).
Stress.	Simple three-stage scale; low/neutral/high (self-report)

Health Coaching will be delivered for eight weeks. Over this period participants will receive a total of six sessions lasting 45 minutes each. Sessions will be delivered by telephone, Skype, Facetime, or in clinic, according to individual preference. At each treatment session the participant and Health Coach will review and set goals to incrementally change lifestyle areas according to need. This kind of semi-structured but flexible approach is consistent with complex interventions shown previously to be efficacious for treating fatigue in cancer, such as exercise[9], cognitive behaviour therapy[11], or yoga.[12] We will take steps to maximise parity of the intervention at all centres.

Arm 3:

Health Coaching plus Patient Activation intervention (n=20). Participants randomised to this arm will be treated as per Arm 2, but will also receive a Patient Activation (PA) intervention. In this intervention a trained PA coach will meet the participant and conduct a standardised semi-structured interview. These trained coaches will be supplied by *brainstrust*, a UK brain tumour charity with considerable experience in the field of personal coaching, and existing in-reach to all three study centres. *brainstrust* will ensure that all coaches delivering this intervention are trained to deliver it in a standardised way.

At the PA interviews participants will complete the Patient Activation Measure (PAM). The PAM is a 13-item measure[26], validated in patients with cancer,[27] that assesses Patient Activation. The focus of this short tool is to provide an initial measure of the participant's knowledge, skill and confidence for self-managing their fatigue. The coaching intervention will then incorporate and leverage this information using the theoretical underpinning of Dilts model of Logical Levels[28], which helps one understand one's health status and make choices about what to do. They will coach the participant to

appropriately leverage their activation to achieve their desired outcomes more effectively. Participants will be offered a second PA interview, identical in structure to the first, after a further four weeks.

4.1 Treatment Schedule

Please refer to Figure 1. In addition:

Acceptability: We will conduct qualitative interviews in a sub-study of 24 participants who were randomised to Health Coaching with or without Patient Activation. These interviews will be co-ordinated by a researcher appointed at the University of Stirling. They will be held within three weeks of the T1 assessment, and will be conducted in all three centres. To ensure reliability of interpretation and coding, data collection and analysis will be supervised by co-applicant MW, a senior and experienced qualitative researcher.

We will use a purposive maximum variation sampling strategy to ensure sample diversity. In this sampling strategy we will consider factors that may be important to the experience of fatigue, for instance sex, age, tumour type, severity of symptoms, whether the intervention included PA or not, type of health coach, and geographical location. We will invite participants to be interviewed in the company of their primary carer and in a location of their preference (e.g. at home). Interviews will investigate participants' experience of Health Coaching. Specifically we will study barriers and facilitators to achieving goals, whether participants found the intervention(s) acceptable or not, and why, and how their experience of fatigue was affected.

These qualitative interviews will draw upon the concept of self-efficacy as a theoretical framework.[29] This theory proposes that perceived ability to manage symptoms is important to achieving optimal symptom management. Self-efficacy is a key concept in the self-management of symptoms in cancer and other chronic illnesses.[30] All interviews will be digitally-recorded on an NHS-encrypted device, transcribed and analysed according to the constant-comparative technique embedded within the overall "Framework" method.[31] Analysis will be facilitated by the use of text management software.

Manageability: The Health Coaches and Patient Activation coaches will record referral waiting times, number and duration of assessments, number and duration of follow-ups, where participants prefer them to occur, number of contacts and their nature, time spent travelling on-study, and total hours spent on-study.

Developing systems and piloting outcome measures: In line with MRC guidance[24] we will take the opportunity to develop and pilot systems and potential outcome measures for a future definitive trial. We will develop and use a structured clinical interview for fatigue, alongside the Brief Fatigue Inventory[32] and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)[33], to study the impairment caused by fatigue over time. We will pilot the Psychological Outcome Profiles (PSYCHLOPS) tool[34] to track progress towards reducing the impact of fatigue on the most important functional outcomes for study participants.. As regards confounding variables, anxiety and depression will be screened using the Hospital Anxiety and Depression Scale[35] while cognitive function will be screened using the Addenbrooke's Cognitive Examination-III (ACE-III).[36] We will record prescribed medication at each study time-point. For all these outcomes we will gather pilot data on the magnitude of effect size in the treatment arms versus control, in order to estimate likely effect sizes in a larger trial.

We may in addition pilot instruments to examine the Health Economic costs and potential benefits of these interventions. We will assess health benefits using the EQ-5D which is the nationally-recommended instrument for this specific purpose.[37]

4.2 Sampling time-points

T0 (baseline): Routine clinic-demographic information from notes review and GP contact, including past medical and psychiatric history, current medications and doses, and physical functional status. Battery of study materials as outlined. T1 (ten weeks post-randomisation): study materials as outlined. T2 (16 weeks post randomisation): study materials as outlined. In addition, qualitative interviews will be conducted on a subset of participants between 10 and 13 weeks post-randomisation (see Figure 1 and Figure 2 below).

Activity	SCREENING	T0 BASELINE	Wk 2- 10 INTERVENTION PHASE	T1 (Wk10) POST-INTERVENTION	T2 (Wk16) ENDPOINT
Brief Fatigue Inventory (BFI)	X			X	X
Patient Written Informed consent	X				
Eligibility Checklist		X			
Medical History		X			
Demographics		X			
Concomitant Medications		X		X	X
Semi-structured Clinical Interview for Fatigue (SCIF)		X			
FACIT Fatigue Scale		X		X	X
PSYCHLOPS Pre-therapy		X			
PSYCHLOPS Post-therapy				X	X
EQ-5D		X		X	X
HADS		X		X	X
ACE-III		X		X	X
Randomisation		X			
Health Coaching Initial Consultation form [1]			X		
Health Coaching appoint-ments [1, 2]			X		
Health Coaching Activity Log [1, 3]			X		
Patient Activation interview [4]			X		
Qualitative interview [1, 5]			X		

Figure 2: *Treatment and Examination Schedule*

1. For patient randomised to Arm 2 or 3 only.
2. Health Coaching will be delivered for eight weeks. Over this period participants will receive a total of six sessions lasting 45 minutes each, by telephone, Skype, or in person (clinic).
3. Participants will record standardised information as often as possible, up to a maximum of each day.
4. For patients randomised to Arm 3 only. PA coach will meet the participant and conduct a standardised semi-structured interview. Participants will be offered a second PA interview, identical in structure to the first, after a further four weeks.
5. Will be conducted in a sub-study of 24 participants within 3 weeks of T1.

4.3 Study materials

All participants will complete (at T0, T1 and T2) the measures outlined under '**4.1: Develop systems and pilot outcome measures'** above. Those receiving Health Coaching will also record data as outlined in the DREEMS model above. Professionals on the study will gather procedural data on recruitment, retention, the technical delivery of Health Coaching, and service use by participants.

4.4 Concomitant Therapy

During the study, participants will be under stable follow-up for a primary brain tumour. Consequently all will have completed primary radiotherapy and/or chemotherapy. Some may continue on routine medications to manage symptoms such as anti-epileptic drugs. Medications and doses will be recorded observationally for clinico-demographic use. No medication will be prescribed or tested as part of this study.

5. SAFETY MONITORING

This is not a trial of a pharmacological compound. We anticipate that the risk of any untoward physical incident as a result of the interventions delivered here is either low, or nil. However brain tumour patients are medically ill, so for completeness and transparency of governance we include the following section. Arguably it is also important because the Health Coaching Intervention is not wholly sedentary: one of the components involves attaining a goal for number of steps taken per day (measured automatically by fitbit-style monitor).

5.1 Definitions

Adverse Event (AE): An adverse event (AE) is any untoward medical occurrence in a study participant which does not necessarily have a causal relationship with the study treatments or procedures. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with a treatment or procedure, whether or not considered related.

Adverse Reaction (AR): All noxious and unintended responses related to a study treatment or procedure should be considered adverse reactions.

Serious Adverse Event (SAE): Defined as any untoward medical occurrence in a participant that:

a) Results in death;
b) Is life-threatening;
c) Requires hospitalisation or prolongation of existing hospitalisation;
d) Results in persistent or significant disability or incapacity, or;
e) Is otherwise considered medically significant by the Investigator

Important medical events may also be considered serious if they jeopardise the subject or require an intervention to prevent one of the above consequences.

The term "life-threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Hospitalisations planned prior to enrolment in the trial or for social reasons will not be considered as SAEs. Treatment in an A&E department of less than 24 hours or on an out-patient basis that does not meet any other serious criteria should not be considered as an SAE.

5.2 Expected events

This section lists those events that are to be regarded as expected for reporting purposes. Note that all are common or potentially common events in patients with a primary brain tumour under normal circumstances.

- Fatigue due to tumour or tumour progression
- Epileptic seizures in a patient with epilepsy, or due to tumour progression
- Functional physical deterioration due to tumour or tumour progression
- Psychological distress due to tumour or tumour progression
- Worsening cognitive impairment due to tumour, tumour progression, or late-delayed radiation reaction
- Tumour progression per se
- Death (due to a complication of tumour)
- Late-delayed radiation reaction
- Pulmonary embolus
- Falls and injury secondary to falls

5.3 Recording of Adverse Events

All adverse events occurring after signing of informed consent through to 30 days after final study procedure will be recorded in the subject's notes and transcribed to the CRF.

Any medical conditions or diseases present prior to signing of informed consent should only be considered an adverse event if there is a worsening of the condition.

5.4 Recording and Reporting of Serious Adverse Events

Contact Details for Reporting SAEs

SCTRU Fax: +44 131 275 7512 (preferred method)
SCTRU Telephone: +44 131 275 7276/ 4278 (Mon – Fri 9am-4pm)

All serious adverse events that occur after the signing of written informed consent and within 30 days after the final study procedure will be recorded on the SAE report form. In addition, any SAE that occurs more than 30 after final study procedure and is deemed to be related to a study procedure should be recorded on the SAE report form. The SAE report form must be signed by the Principal Investigator of the centre involved and faxed to SCTRU within 24 hours of the Investigator first becoming aware of the event. All initial SAE reports should contain the following minimum information:

- Reporter details
- At least one suspect procedure
- At least one subject identifier (trial number/patient initials)
- Adverse Event term
- Causality assessment

A fax receipt will be sent to the relevant centre by SCTRU to acknowledge receipt of the SAE report form, and SCTRU will notify the Chief Investigator (CI) The sponsor will be notified of all SAE's which occur in the form of a line listing which will be sent to them by SCTRU every 2 months.

Any SAE that has been assessed as related will be forwarded to the CI by SCTRU. Any SAE that is deemed to be both **related (**ie resulted from administration of any of the research procedures) and **unexpected (**ie not listed in the protocol as an expected occurrence) will be notified to the Research Ethics Committees within 15 days of the CI becoming aware of the event

Related and unexpected SAE's should be reported to the REC using the 'Non-CTIMP safety report to REC form'. This should be signed by the CI and include a statement on the assessment of the implications, if any, for the safety of study participants and how will these be addressed. The coordinator of the REC should acknowledge receipt of the safety report within 30 days. The MHRA do not require to be notified of SAEs within this trial, as the study does not involve the use of an investigational medicinal product. http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/. SCTRU will notify the PI's at all of the participating centres of the occurrence of any related and unexpected SAE's

There is no requirement to submit annual safety reports to the REC in addition to the information provided through the annual progress report.

5.5 Pregnancies

Any pregnancy in a trial participant that occurs during study participation should be reported to SCTRU within 24 hours of the site RA or PI becoming aware of its occurrence, using the contact details in Section 5.3. The SCTRU will ensure that the information is passed to the relevant Health Coach to make them aware.

6. DATA MANAGEMENT

All data will be handled, computerised and stored in accordance with the Data Protection Act 1998 and NHS National Services Scotland Confidentiality Guidelines.

6.1 Data Collection

Health coaching:

At the first health coaching session, participants will be given a home diary to record their progress. The health coach will initiate a secure end-to-end NHS.net-based email thread, by emailing the participant's preferred email address from an nhs.net account, with their study code number and "[Secure]" in the subject line. All study email communication between the health coach and the participant will use this encrypted Study Thread. At intervals by agreement, the participant will take a clear picture of their completed home diary on their smartphone. They will access their email account and email the health coach on the secure Study Thread, attaching the picture of their diary. In this way the health coach will gather data securely, with minimal effort for participants and without the need for a third-party app or the posting of hard copies of the diary. Follow-up appointments will be guided by these securely-emailed images of the participant's home diary. After the appointment the health coach will forward the diary image via nhs.net to the RA/RN for data entry.

Alternatively, participants may choose to attend follow-up in person. In this case they will simply be asked to bring their diary with them to the appointment. The health coach will use the diary to guide the appointment. At the end of the appointment the health coach will scan the diary and save the image file on an NHS Lothian-encrypted memory stick. They will then use nhs.net to email the image file to the RA/RN for data entry. Once acknowledged by the RA/RN, the scanned image file will be deleted from the memory stick.

Patient activation:

The Patient Activation interviews will not be audio-recorded. The coaches will not take written notes during the interview. Immediately after the interview, the patient activation coach will write an email, send to the RA/RNvia nhs.net, summarising the interview. The RA/RNs will upload the text to the central study database.

At site:
Data generated from T0, T1 and T2 interviews will be collected at site, The data will then be checked and validated by SCTRU. The data collected will include:

- initial clinical details at randomisation
- concomitant medications
- adverse events
- survival
- withdrawal
- protocol deviations

6.2 Record Keeping and Archiving

Study documentation will be retained at site until the end of follow up. The documentation will then be archived using an NHS-approved service, according to current legislative requirements.

7. STATISTICS

7.1 Sample Size

60 participants will be randomised to one of three study arms:
- Control (n=20);
- Health Coaching (n=20);
- Health Coaching plus Patient Activation intervention (n=20).

7.2 Power considerations

In line with NIHR guidance[25] this study is neither intended nor powered to study the efficacy of Health Coaching. Rather our sample size of 60 patients (20 patients per group) is based on what is reasonably sufficient to study feasibility. Equally the subsample of 24 patients who will receive a qualitative interview is in line with accepted practice in the qualitative research field.

7.3 Exit strategy to a definitive trial

We will develop systems, relationships, and experience in the three centres necessary to running a definitive trial. We will in particular pilot the FACIT-F scale[33] as a possible primary outcome measure, given that it is a frequently used fatigue scale for which validated minimal clinically important differences have been published. We have additionally conducted a power calculation to illustrate the capacity for a definitive trial. Assuming: (1) a standard 2-arm RCT and 1-1 randomisation schedule; (2) a typical standard deviation in the FACIT-F of SD=12; (3) Alpha (p)= 0.05, then in order to have 90% power to detect a minimal clinically important difference in the FACIT-F of 8 points, we would require n=49 participants per arm. The current feasibility study will inform us further about rates of recruitment and attrition, and likely effect sizes. Given the prevalence of fatigue in patients with a brain tumour, and because we will pilot systems over a wide geographical catchment, we see a viable exit strategy from this feasibility study.

7.4 Analysis Plan

Final analysis will be performed at the end of the study, i.e. when all patients have completed their assessments and all data has been cleaned and the database locked.

Statistical quality assurance will be carried out to correct spurious data and to mimimise the level of missing data.

Analysis will be carried out on all patients randomised to the study.

Number of patients recruited over a 12 month period will be tabulated overall by site and treatment arm. This will be compared to the target of 20 patients.

Number and proportion of patients retained within the trial to the T2 endpoint (16 weeks after randomisation) will be tabulated overall and by site and treatment arm. This will be compared to the target that at least 60% of patients will be retained until the T2 endpoint.

The mean change (from baseline to 16 week follow up) in outcome scale scores with 95% confidence intervals will be calculated for each treatment arm.

7.5 End of Study

The End of Study will be performed when all patients have completed their assessments at the end of the 16 week follow up and all data has been cleaned and database finalised.

8. ACCESS TO SOURCE DATA/ DOCUMENTS

The investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the Sponsor, SCTRU or the Coordinating Centre, or regulatory authorities, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital patient charts and other study files) to these authorised individuals.

9. QUALITY CONTROL AND QUALITY ASSURANCE

Quality control will be maintained through adherence to the Principles of ICH GCP (Appendix 3) and the SCTRU or coordinating centre's SOPs. The coordinating centre will monitor receipt of CRFs and evaluate incoming CRFs for compliance with the protocol, inconsistencies and missing data.

9.1 Monitoring Visits

There will be no monitoring visits performed for this study.

9.2 Data Monitoring and Ethics Committee

An independently-chaired Data Monitoring Committee (DMC) will be established and will meet 6 monthly in the first instance and annually thereafter (and at any other time at the committee's discretion). There will be an extra meeting of the committee after 13 patients have been recruited. The committee will receive regular reports from SCTRU. It will submit its comments and recommendations to the Trial Steering Committee (TSC) and Trial Management Group (TMG). The DMC will be chaired by **Prof. Anthony Byrne** (University of Cardiff).

9.3 Trial Steering Committee

An independently-chaired Trial Steering Committee will be established to provide overall supervision of the trial, in particular; trial progress, adherence to protocol, patient safety, and consideration of new information. The committee will meet 6 monthly in the first instance and then 6 monthly thereafter. The committee will then meet 3 monthly during close out/ final analysis. The TSC will be chaired by **Prof. Martin Klein** (Vrie Universiteidt Medisch Centrum, Amsterdam).

10. ETHICAL CONSIDERATIONS

Ethical approval by a Research Ethics Committee will be obtained before the trial is started. The trial will be carried out according to guidelines of good clinical practice (GCP) as defined by paragraph 28 and Schedule 1 Part 2 of the Medicines for Human Use (Clinical Trials) Regulations, 2004, and the Clinical Trials Directive (2001/20/EC) elsewhere in the European Union and follow the principles of research governance.

10.1 Participant Confidentiality

The participant's full name, date of birth and hospital number will be collected to enable tracing through national records. The personal data recorded on all records will be regarded as confidential, and to preserve anonymity, only the trial number and initials will be recorded on CRFs.

The PI (or delegate) at each site will keep a log of the site's participants' trial numbers, names, addresses, email address, phone number(s) and hospital numbers. The PI must ensure that confidentiality is maintained and that all trial documents (e.g. consent forms) are maintained in strict confidence.

SCTRU will maintain the confidentiality of all data and will not reproduce or disclose any information by which participants could be identified. Participants will only be referred to by trial number and initials in any essential trial related correspondence, including Case Report Forms and Serious Adverse Event Reports.

All patient-identifiable data will be handled, computerised and stored in accordance with the Data Protection Act 1998 and NHS National Services Scotland Confidentiality Guidelines.

10.2 Informed Consent

All participants will be informed of the aims of the study, the procedures and possible hazards to which they will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician. It will be emphasised that the participation is voluntary and that patients are allowed to refuse further participation in the protocol whenever they want. This will not prejudice their subsequent care.

Documented informed consent will be obtained for all participants in the study before they are enrolled. This will be done in accordance with the national and local regulatory requirements and will conform to guidelines on Good Clinical Practice. That is, "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

Copies of the Patient Information Sheets and consent forms are provided in the supporting materials accompanying this protocol.

All Patient Information Sheets & Informed Consent Forms will be version controlled and dated and this information will always be stated in any communication with ethics committees.

11. RESEARCH GOVERNANCE

Sponsor (NHS Lothian) – NHS Lothian will act as study sponsor, with co-sponsorship from The University of Edinburgh . The sponsors will have overall responsibility for the design, co-ordination and management of the study. These include:

- Trial authorisation including responsibility for the protocol and obtaining approvals
- Ensuring that the trial is conducted according to GCP guidelines (22,23)
- Review of SAEs

Clinical Trials Unit – The sponsor has delegated the responsibility for overall project management, data management and monitoring to Scottish Clinical Trials Research Unit, NHS National Services Scotland. Responsibilities include:

a. Assistance with completion of the IRAS form and REC communication
b. Production of trial specific documentation (i.e. CRFs)
c. Facilitating set up of trial centres
d. Data management
e. Monitoring
f. Safety Monitoring

Central study co-ordination, data collection, monitoring and organisation of the data for the statistical analyses will be undertaken by the Scottish Clinical Trials Research Unit, NHS National Services Scotland, which has processes in place to ensure that the study will not open to recruitment until appropriate approvals and authorisations have been obtained from an independent research ethics committee, and NHS Research and Development departments (R&D).

Statistical Analysis – A Principal Information Analyst (Robert Hill), based at SCTRU, Edinburgh will undertake the final analysis arising for this study.

Local Project Teams – These will consist of a consultant Surgeon, Oncologist, Neurologist, or Clinical Nurse Specialist (responsible for introducing the patient to the study and partially ensuring eligibility), and a Research Assistant (responsible for co-ordination of all aspects of data collection). Centres are specifically responsible for conducting the trial in accordance with the protocol, Standard Operating Procedures (SOPs), the trial agreement and Good Clinical Practice.

Trial Steering Committee and Data Monitoring and Ethics Committee –. The Trial Steering Committee (TSC), including members of the research team, a statistician, and lay representation, will be responsible for the progress and conduct of the study. A Trial Management Group (TMG) will meet quarterly. A Data Monitoring and Ethics Committee (DMC) will convene as outlined above, to review all data. Specific issues that will be looked at include: recruitment, retention, tolerability of Health Coaching, withdrawals of consent, schedule reductions, and adverse events.

12. FINANCING AND INSURANCE

This study is wholly funded by The Brain Tumour Charity. Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

13. PUBLICATION POLICY

All presentations and publications relating to the trial will be authorised by the Trial Management Group. The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all Collaborators. The manuscript will be prepared by the Trial Management Group, representatives from SCTRU, NHS National Services Scotland, and high accruing clinicians. The trials offices and all participating Centres and clinicians will be acknowledged in this publication. Any data that might detrimentally affect the progress of the trial will not be released prior to the end of the trial. No investigator may present or attempt to publish data concerning participants, which is directly relevant to the questions posed in the trial, until the main results have been published.

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Appendix 1a – Investigator Statement (SCTRU Copy)

BT-LIFE

Brain Tumours, Lifestyle Interventions, and Fatigue Evaluation

Principal Investigator Declaration

I acknowledge receipt of version <#> date <dd/mmm/yyyy> of the BT-LIFE trial protocol (REC approved <dd/mmm/yyyy>) and I agree to perform this trial in accordance with this version of the protocol and Good Clinical Practice.

I understand that the safety of the patient is my first concern.

Print Name: ----------

Hospital: ----------

Signed: ----------

Date: ----------

Please return this copy to: BT-LIFE Trial Coordinator
Scottish Clinical Trials Research Unit,
Gyle Square,
1 South Gyle Crescent,
Edinburgh,
EH12-9EB

Appendix 1b – Investigator Statement (Investigator Copy)

BT-LIFE

Brain Tumours, Lifestyle Interventions, and Fatigue Evaluation

Principal Investigator Declaration

I acknowledge receipt of version <#> date <dd/mmm/yyyy> of the BT-LIFE trial protocol (REC approved <dd/mmm/yyyy>) and I agree to perform this trial in accordance with this version of the protocol and Good Clinical Practice.

I understand that the safety of the patient is my first concern.

Print Name: ----------

Hospital: ----------

Signed: ----------

Date: ----------

Please retain this copy and file in Investigator Site File

Appendix 1c - The Principles of ICH Good Clinical Practice

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/ favourable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. This principle applies to all records referenced in this guideline, irrespective of the type of media used.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented. Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

Appendix 1d - Schedule for Health Coaching intervention

1. Following informed consent and before the first Health Coaching appointment

The Research Assistant/Research Nurse will provide the participant with a diary to record data by hand.
Participants will be asked to start recording lifestyle information before their first Health Coaching appointment.
A Health Coaching 'Consultation Form' will be given to all participants to complete.

2. At the first Health Coaching appointment (face to face in clinic)

Discuss Consultation Form.
Initial assessment – measure % body fat, blood pressure, body mass index / perform basic biomechanics screening to establish physical ability.
Introduce muscle activation exercises.
Discuss lifestyle data already gathered.
Set goal(s) for week ahead.
Participant and Health Coach will organise the next follow up appointment and type (face to face, Skype, phone).

3. Between appointments

Participants to record lifestyle information, using the home diary. Information should be recorded as often as possible but it is not essential that it is recorded every day, if this is difficult.
Participants will receive regular reports on progress from their Health Coach.
The Health Coach will record manageability data in the Health Coach Manageability Log.

4. Follow up appointments (in clinic/home/phone/skype)

The Health Coach will review recorded lifestyle information recorded since the previous appointment.
New goal/s will be set as appropriate. Participants will be encouraged to maintain goals already in place from the previous appointments.
Participants will be able to ask questions and concerns. These will be recorded by the Health Coach to inform our understanding of the acceptability of the intervention.

APPENDIX: Lifestyle Information recorded during Health Coaching

Participants will record standardised lifestyle information daily into a home diary ,

Participants will record lifestyle information on Drink, Rest, Eating, Exercise, Movement and Stress (DREEMS). The recording of each behavioural component of DREEMS is explained below.

Lifestyle Information (DREEMS)

Drink**:** The number of each daily fluid item (water, milk, juice, tea, coffee and alcohol) will be self-reported daily in the Nudge app or the custom design form.

Rest: Total sleep time (hours per day) will be self-reported in the Nudge app or the Custom Design Form.

Eating**:** Food items will be self-reported in the app or Custom design form. Food items measured include Protein, Fruit, Vegetables, Dairy, Legumes, Nuts, Healthy Fats, Starches and Indulgent food items. These food items can be tailored suit to the participant's diet.

Exercise: Frequency and duration of exercise sessions will be recorded in the app or the Custom Design Form.

Movement**:** Total number of steps taken per day will be recorded objectively by a fitbit-style monitor. The data retrieved will be synced to the app, or written into the custom design form by hand.

Stress: Stress will be self-reported using a simple three-stage scale; low/neutral/high. This data will be reported in the app or the custom design form.

Appendix 1e - Schedule for Patient Activation intervention

Following informed consent and allocation to Group 3

- The recruiting Research Assistant/Research Nurse will seek the participant's preference of location of Patient Activation: at home, Skype, telephone, or facetime.
- The Research Assistant/Research Nurse will liaise with *brainstrust* and the participant to arrange the time of the first session. This will be scheduled to occur after the first Health Coaching session.

First Patient Activation session

1. The Patient Activation coach ("the coach") will meet with the participant as arranged, and discuss the aims and use of PA in the context of fatigue and the study.
2. The coach will survey the participant's current level of Activation by administering the PAM-13 Patient Activation measure. This will be by physical copy for face-to-face coaching, or verbal transcription for distance coaching.
3. Discuss the PAM-13 results and use them to guide the intervention.
4. The coach will lead the participant through the semi-structured "Dilts' Logical Levels" schedule (see Appendices), focusing on increasing the participant's skills, knowledge and confidence to manage their own fatigue.
5. Agree suitable goal(s) for the participant to aim for.
6. Arrange next coaching session date and location preference.

Between sessions

- The Coach will make notes of their session content and store these, anonymised, on an encrypted NHS memory stick.
- Participants receiving Patient Activation will not be asked to keep a diary of any specifications with respect to PA, between sessions.
- If they choose, they will be able to contact the PA coach to discuss questions between sessions. The PA coach will keep an anonymised record of any such participant-initiated contact using an encrypted NHS memory stick.

Second Patient Activation session (c. 4 weeks after first)

1. General discussion of progress since last session.
2. Administer the PAM-13 and discuss any changes between coaching sessions one and two.
3. Apply the FRAME (Feedback, Responsibility, Advice, Menu, and Efficacy) approach to enhance patient self-efficacy in managing their fatigue.
4. Elicit any problems using G.R.O.W. (Goal, Reality, Options, Way forward), to explore options and articulate ways forward.

APPENDIX: Supporting material for Patient Activation intervention

Patient Activation Measure (PAM-13) questions and underlying rationale (used in sessions one and two)

1. When all is said and done, I am the person who is responsible for managing my health condition.
2. Taking an active role in my own health care is the most important factor in determining my health and ability to function.
3. I am confident that I can take actions that will help prevent or minimise some symptoms or problems associated with my health condition.
4. I know what each of my prescribed medications do.
5. I am confident that I can tell when I need to get medical care, and when I can handle a health problem myself.
6. I am confident I can tell my health care provider concerns I have, even when he or she does not ask.
7. I am confident that I can follow through on medical treatments I need to do at home.
8. I understand the nature and causes of my health condition(s).
9. I know the different medical treatment options available for my health condition.
10. I have been able to maintain the lifestyle changes for my health that I have made.
11. I know how to prevent further problems with my health condition.
12. I am confident I can figure out solutions when new situations or problems arise with my health condition.
13. I am confident that I can maintain lifestyle changes like diet and exercise even during times of stress.

Lower levels of Patient Activation may indicate:

- A lower level of knowledge and skills in managing fatigue / health coaching;
- Participant may benefit from taking smaller steps;
- Participant may not understand causes of fatigue or how lifestyle changes may work;
- Participant may not have confidence in their ability to complete health coaching;
- A menu of options, empathetic reflections, and empowering affirmations may benefit.

Higher levels of Patient Activation may indicate:

- A higher level of knowledge, skills, and confidence;
- Participant may or may not resent someone telling them what to do;
- Participant may have strong opinions about treatment options and may have already researched ways to improve fatigue;
- Participant may be used to success – potential cause of frustration if progress is not as hoped;
- Supporting their autonomy may benefit.
- Participants with lower PA may benefit from greater direction from a coach, while those with higher PA may require less direction and benefit from a greater focus on autonomy. Therefore, measuring Patient Activation will guide how the coach approaches each session.

Dilts' Logical Levels framework and exemplars (used in session one)

Purpose

What do you think health coaching aims to achieve?
Do you think it will have an effect on your fatigue?
What is your hope/desire to achieve by taking part in this project?

Identity

What do you see as your role in health coaching?
Do you consider yourself to be a person who is interested in their health?

Values

How important is it to you to complete health coaching to your best ability?
Do you believe that health coaching will help your fatigue?
Do you feel that your health coach is important in achieving your goals?

Capabilities

How confident are you in achieving the goals and tasks set out by your health coach?
What will you need to complete health coaching to your best ability?
What bits of HC are you looking forward to tackling the most/least?

Behaviours

Can you think of things you might do to help you complete health coaching?
Are there any current activities that might not be productive in completing health coaching?
Has the health coach suggested any activities that you've already thought about doing?

Environment

Who or what in your environment do you think will be important in achieving your goals?
Is there anything in your environment that you find particularly exhausting?
Can you think of things that help reinvigorate you?

F.R.A.M.E. framework and exemplars (used in session two)

Feedback

Discuss the lowest rated items on the PAM-13. *E.g.* If the participant registered a low score on Item 9, the coach might open a discussion of the perceived importance *to the participant* of knowing about different treatment options.

Responsibility

Assess the participant's perceived personal responsibility in improving knowledge/confidence. *E.g.* If they do not perceive themselves to have responsibility, the coach might seek to increase their level of Patient Activation by asking the participant about the pros and cons of their current approach.

Advice

Collaborative goal-setting in relation to the lowest PAM-13 score(s).

Menu

Discuss the menu of options for self-management relating to issues discussed in *Feedback* section:
- Start with what the participant feels comfortable aiming for in the short term.
- Move on, if suitable, to longer-term goals.

Efficacy

Enhancement strategies for self-efficacy:
- Use previous successes to motivate new advances in their health.
- Break goals into attainable steps
- How can they take the initial steps to achieve this?
- What support will they need?
- Who can help them?

G.R.O.W. framework and exemplars (used in session two)

Goal

Discuss the goal from first session and any progress in achieving it.

Reality

What has happened in achieving the goal?
Have they got any closer in certain aspects – has anything been put back?
Is this goal still realistic?
What has stepped in the way of the goal?

Options

What has changed/developed that we can apply to achieving the goal?
Are there any recent developments?
Brainstorm possible options to achieving goals.
What is still a limiting factor in your recovery/ability to achieve your goals?
What if this constraint was removed?
Way forward

What is still driving you to make these changes?
What will you do now?
When would you like to do it?
What might set you back
How would you tackle this?