Integrated rehabilitation for thoracic cancer

# Short term integrated rehabilitation for people with thoracic cancer: A feasibility trial

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## KEY ROLES AND RESPONSIBILITIES

**SPONSOR:** The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

**FUNDER:** The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

**CHIEF INVESTIGATOR (CI):** The person who takes overall responsibility for the design, conduct, monitoring and reporting of the study. As the study involves researchers at more than once site, the CI takes on the primary responsibility though she is not the principal investigator at any of the sites.

The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. The CI will also ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the R&I Office of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

**PRINCIPAL INVESTIGATOR (PI):** Is the person who takes responsibility for the conduct of the research at each site. Their role is to ensure that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

## DECLARATIONS

THE UNDERSIGNED CONFIRM THAT THE FOLLOWING PROTOCOL HAS BEEN AGREED AND ACCEPTED AND THAT THE INVESTIGATOR AGREES TO CONDUCT THE STUDY IN COMPLIANCE WITH THE APPROVED PROTOCOL AND WILL ADHERE TO THE RESEARCH GOVERNANCE FRAMEWORK 2005 (AS AMENDED THEREAFTER), THE TRUST DATA & INFORMATION GOVERNANCE POLICY, SPONSOR AND OTHER RELEVANT SOPS AND APPLICABLE TRUST POLICIES AND LEGAL FRAMEWORKS.

I (INVESTIGATOR) AGREE TO ENSURE THAT THE CONFIDENTIAL INFORMATION CONTAINED IN THIS DOCUMENT WILL NOT BE USED FOR ANY OTHER PURPOSES OTHER THAN THE EVALUATION OR CONDUCT OF THIS RESEARCH WITHOUT THE PRIOR WRITTEN CONSENT OF THE SPONSOR.

I (INVESTIGATOR) ALSO CONFIRM THAT AN HONEST ACCURATE AND TRANSPARENT ACCOUNT OF THE STUDY WILL BE GIVEN; AND THAT ANY DEVIATIONS FROM THE STUDY AS PLANNED IN THIS PROTOCOL WILL BE EXPLAINED AND REPORTED ACCORDINGLY.

CHIEF INVESTIGATOR:

SIGNATURE: .....JO BAYLY..... DATE: 27/11/2017

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POSITION: HEE/NIHR CLINICAL DOCTORAL RESEARCH FELLOW

# Contents

# 1 List of abbreviations

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|---|---|
| AE | Adverse Event |
| CI | Chief Investigator |
| CRF | Case Report Form |
| GAfREC | Governance Arrangements for NHS Research Ethics |
| GCP | Good Clinical Practice |
| HRA | Health Research Authority |
| ICF | Informed Consent Form |
| ISF | Investigator Site File |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| MPM | Malignant Pleural Mesothelioma |
| NSCLC | Non-Small Cell Lung Cancer |
| PI | Principal Investigator |
| PIS | Participant Information Sheet |
| PPI | Public & Patient Involvement |
| QA | Quality Assurance |
| QC | Quality Control |
| RCT | Randomised Controlled Trial |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SDV | Source Document Verification |
| SOP | Standard Operating Procedure |
| SCLC | Small Cell Lung Cancer |
| TMG | Trial Management Group |

Trial personnel


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| Dr Andrew Wilcock[2] | Co-applicant | Physician, trials, palliative care, lung cancer |
| Ms Caroline Murphy[4] | Collaborator | Trial management, trial coordination, palliative care nurse |

# 2 Summary

| STUDY OVERVIEW | |
|---|---|
| Full title | **Short term integrated rehabilitation for people with thoracic cancer: A feasibility trial** |
| Objectives | **Primary Objective:**<br>To identify the acceptability and feasibility of recruiting people with thoracic cancer to a trial of a rehabilitation service trial over a twelve-month period.<br>**Secondary Objectives:**<br>1. To identify acceptability and feasibility of delivering the rehabilitation service over 1-3 contacts over 30 days<br>2. To evaluate performance of selected clinical outcome measures<br>3. To obtain recruitment rate to estimate sample size for a full trial<br>4. To evaluate trial procedures<br>5. To evaluate fidelity of service delivery and uptake of discrete service components<br>6. To describe pattern of ongoing referrals to local rehabilitation services<br>7. To identify and describe use of other health care resources during trial period |
| Type of trial | A parallel group 1:1 randomised, controlled multicentre feasibility trial |
| Trial design and methods | Following the MRC guidance for the development and evaluation of complex interventions we will conduct a randomised controlled feasibility trial of short term rehabilitation (a complex intervention) offered by a specialist allied health care professional compared to best standard care.<br>Outcomes will evaluate feasibility parameters, including the acceptability of the trial processes and outcome measures and the rehabilitation service components and processes:<br>1. Proportion of eligible participants randomised<br>2. Proportion of randomised patients remaining on trial for 30 days for 1, 2 and 3 contacts; reasons for drop out<br>3. Recruitment rate<br>4. Response and completion rates to outcome measure questionnaires with reasons for missing data.<br>a. Integrated Palliative Care Outcome Scale<br>b. Physical Activity Scale for the Elderly (PASE)<br>c. Self-Efficacy Measure Chronic Disease (SEMCD)<br>d. Functional Assessment of Cancer Therapy Lung-Trial Outcome Index (FACT-L TOI)<br>e. Client Services Receipt Inventory |

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| | f. EQ-5D-5L<br>g. Patient experience of trial participation (including FACIT-TS-PS)<br><br>5. Intervention fidelity:<br>a. number of planned contacts per participant, mode of contact, proportion of participants with a rehabilitation plan<br>b. proportion of patients & carers receiving support to:<br>i. self-manage symptoms<br>ii. maintain physical activity and fitness<br>iii. maintain task performance and participation in activities<br>iv. onward referrals<br>6. Frequency and type of discrete Behaviour Change Techniques used during intervention delivery |
| Health condition(s) or problem(s) studied | Non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC) and MPM (for purposes of this protocol the term thoracic cancer is used for all three conditions) |
| Target sample size | 60 (30 in each arm) |
| Trial duration per participant: | The length of intervention is usually 60 days from referral<br>• Baseline = Consent, baseline measures, randomisation<br>• Days 1-30 = x3 contacts with AHP OR usual care<br>• Day 60 = Follow- up measures |
| Main inclusion/exclusion criteria: | **Inclusion criteria:**<br>• Age >18 years<br>• Clinical or histological diagnosis of NSCLC, SCLC or MPM, within the last 8 weeks<br>• ECOG performance status 0-3<br>• Ability to respond to questions in written English – or availability of interpreters to enable this<br><br>**Exclusion criteria:**<br>• Co-existing progressive neurological condition (e.g. multiple sclerosis, motor neurone disease)<br>• ECOG performance status 4 (due to association with short survival)<br>• Inability to complete patient questionnaires due to cognitive impairment, or language difficulties and lack of interpreters<br>• Patients currently receiving specialist rehabilitation, or planned to receive within the next month<br>• Receiving palliative care with expectation of death within 1 month |

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| Statistical methodology and analysis: | Single analysis of follow up data from 60 recruited participants.<br>Baseline characteristics will be summarised.<br>• Proportion of eligible patients approached randomised- overall & by recruitment setting and diagnosis<br>The following outcomes will be summarised overall and by trial arm, with corresponding 95% confidence intervals:<br>• Proportion of patients remaining in study for 30 and 60 days<br>• Proportion of missing data will be summarised overall and for each trial outcome, at each time point of assessment<br>Reasons for missing data (where available)<br>Treatment fidelity and contamination will be summarised by number of patient contacts, number of patients seen with carer, mode of contact, proportion of patients with a rehabilitation plan, content of rehabilitation plan (coded under symptom self-management; physical activity/fitness; task performance/participation in ADL), number of manualised behaviour change techniques used per intervention, by treatment arm. |
| **STUDY TIMELINES** | |
| Study Duration/length | 12 months |
| Expected Start Date | October 1st 2017 |
| End of Study definition and anticipated date | September 30th 2018 |

# 3 Background and Rationale

**Thoracic cancer**

Lung cancer is the most frequently diagnosed cancer in men worldwide, with prevalence in women second only to breast cancer(1) and the number of people with malignant pleural mesothelioma (MPM) continues to rise annually, with more than 2000 new diagnoses in 2011.(2) Despite functional and daily living needs being less well represented in the supportive care literature, it is recognised that thoracic cancers and their medical treatment (with chemotherapy, radiotherapy and surgery) do affect day-to-day life. (3-6) Approximately ten percent of patients with non-small cell lung cancer (NSCLC) are treated curatively with surgery.(7) Surgery is not indicated in the treatment of small cell lung cancer (SCLC) and current MPM treatment guidelines recommended radical surgery is only offered within the context of a clinical trial.(5) Most patients will receive single modality or combination treatment with chemotherapy, radiotherapy, targeted therapy or immunotherapy.(8, 9)

People with thoracic cancers experience multiple symptoms, psychosocial distress and functional impairments relating to the disease itself, comorbidities and the consequences of treatment. The symptom burden includes breathlessness, fatigue, cough, pain, depression and sleep disturbance.(10-12) S  can cause distress at low levels of intensity.(13) Needs are often complex and impact on multiple domains including treatment tolerability(14), use of health care resources(15) day-to-day living, independence and overall quality of life from diagnosis.(3, 5, 6) Daily life is also affected by reduced physical functioning which precedes and progresses during cancer treatment.(16) The disclosure of diagnosis has been associated with a reduction in physical function in the absence of worsening symptoms.(17) Cancer cachexia and sarcopenia, which adversely affect muscle function, are highly prevalent in people with NSCLC(18, 19) and MPM.(20) Nevertheless, people strive to live as normal.(21, 22) In a UK national survey of people with thoracic cancer, nine out of every ten respondents stated that it was 'important or very important' for them to be able to continue with everyday tasks after treatment.(23) People want to know what they can do to help themselves manage symptoms, daily living and getting well.(3, 4) Practical help is sought and valued.(24)

**Rehabilitation in thoracic cancer**

The theoretical case for rehabilitation in advanced cancer to decelerate the disabling impact of the disease and treatments, optimize function, and promote independence is established.(25-27) UK national guidelines recommend that patients with cancer are able to access rehabilitation, whenever they need it at any point of the treatment pathway from diagnosis.(28) Rehabilitation interventions for the self-management of symptoms, such as breathlessness and fatigue have demonstrated effectiveness in patients with advanced disease (29, 30) and thoracic cancer(31-33)  but the acceptability of such interventions for patients commencing treatment or who are not yet reporting symptoms is uncertain.(34, 35) Exercise, physical activity and dietary counselling rehabilitation interventions, as part of a multi-modal treatment strategy, may relieve disease and treatment associated muscle wasting(36, 37) and help people stay active and independent.(38, 39) Although acceptable to some patients,(40) it cannot be assumed in a context of uncertain disease progression that interventions such as exercise programmes would be acceptable or effective to all.(41-44) However, where a clear benefit is perceived to be attainable, acceptability increases.(34) Further, the structure provided be rehabilitation may attenuate the negative effects of uncertainty experienced by patients at this time.(47)

Qualitative studies demonstrate that patients want information and support to manage symptoms, continue with everyday activities, and to know how to help themselves.(21, 22) However, barriers and enablers at the level of the patient, clinician and healthcare system reduce the acceptability and accessibility of rehabilitation services. These include physical and psychological factors relating to the disease, treatment and co-morbidities, beliefs about benefits, harms or burden of rehabilitation

and access to information, pre-morbid physical activity behaviours, general affect and motivation. The mode, location and format of services influences uptake as do attitudes and values within families and healthcare teams.(27, 45-49) Some people prefer to utilize their own resources.(43)

**Why this research is needed now**

NHS England recommend that rehabilitation be offered to patients with cancer in the period following diagnosis(50) and UK national guidelines for the management of lung cancer recommend rehabilitation needs are assessed as part of holistic needs assessment.(51)

Despite these recommendations, patients newly diagnosed with thoracic cancer face difficulties accessing rehabilitation services.(52) The reasons for this vary but include lack of service provision, oncologists not recognizing functional deficits, reluctance from patients to discuss functional impairment with their oncologist (for fear it may impact on which treatments are offered) and a tendency for referrals to only take place once the patient has become dependent.(25)

This research aims to address gaps identified in the literature. It can be hypothesised that rehabilitation delivered soon after diagnosis would decelerate the functional decline experienced by people with thoracic cancer. The short-term approach proposed in this trial should enable more patients to access rehabilitation within current levels of AHP staffing. This is important to explore, as the increasing size of the cancer population(53) will create a need for more efficient and co-ordinated services in specialist settings. Providing proactive support around the time of diagnosis will provide a route to consecutively screen patients (54, 55)and shift the focus of rehabilitation towards maintaining (rather than regaining) function, which requires less of a behaviour change and can be achieved through a self-management approach.(37) Further, if the service can be better integrated into the existing health care system, this will enable continuity of rehabilitation provision by the main care provider, often an oncologist or nurse specialist.(56) This fits within the specialist service remit to work with generalists directly, at times of need, and indirectly through sound education and support of other professionals. This level of integration occurs in some specialist cancer centres where an AHP is a core members of the team, but is limited in most acute hospital settings.(57)

**Justification for randomised feasibility trial**

We propose that a short-term, integrated rehabilitation service for people with newly diagnosed thoracic cancer will result in better symptom control, improved function for patients, improved coordination of care, more efficient use of existing resources and potentially a reduction in overall service use through increase independence at home, e.g. reducing hospital stay and impacting on place of death.

However, before the effectiveness of this model of rehabilitation can be tested, the feasibility of conducting a randomised controlled trial and the acceptability of the trial and intervention procedures to patients and health care professionals in the period following diagnosis needs to be established. Similar models are being developed to provide specialist palliative care services to the frail elderly and patients with neurological(58) respiratory conditions,(29) with emerging evidence supporting effectiveness and cost effectiveness. The Cochrane Handbook outlines that if there is empirical evidence that similar interventions have an impact, or identical interventions on other populations, these are quite likely to have effectiveness.(59, 60) Thus, as a starting point it is reasonable to hypothesise that the short term integrated rehabilitation service will help people with thoracic cancer.

However, the acceptability of individualised rehabilitation services to minimise the impact of diagnosis and treatment on participation in daily life activities has not been tested in the period following diagnosis. Patient and organisational uncertainties remain to be explored. Previous qualitative studies highlight person and health care system level barriers to patients accessing and participating in rehabilitation. Uncertainties surround the timing, location and content of

rehabilitation interventions delivered in the period following diagnosis when patients are coming to terms emotionally with their new life situation at the same time as undergoing a busy and potentially arduous oncology treatment schedule.(34, 35, 61) Furthermore, it is not known which outcomes should be used to evaluate rehabilitation interventions in this population the period immediately following diagnosis as treatment commences.

The rehabilitation service we are modelling is a complex intervention offered in a heterogeneous population and involves a range of active components, behaviours and target outcomes in the delivery of individualised treatment modalities and self-management strategies. Integration with care delivered by other provider adds a further layer of complexity. In line with recommendations from the UK Medical Research Council Framework for the Development of Complex Interventions the trial forms part of a mixed methods study incorporating both qualitative and quantitative methods.(62) This approach is suited to the development of complex interventions in populations of patients with advanced illness.(63)Pre-trial development work has included systematic review and a focus group study. The review, (in preparation for submission for publication) has informed the incorporation of behaviour change techniques to enhance the delivery of service components in this population. Focus groups held with groups of clinicians and people with experience of living with thoracic cancer supported the justification and rationale for the trial. Participants reported that people who are recently diagnosed do experience significant challenges to their ongoing function in daily life and that these are potentially modifiable by rehabilitation interventions. However, they expressed uncertainty regarding how the service could be delivered to meet the need of all patients. The uncertainty related to patients' co-morbidities, beliefs and priorities, individual responses to diagnosis, treatment schedules, responses to treatment, timing, location and mode of delivery of the service. Equipoise was demonstrated and the data informed the development of the trial components and procedures.

# 4 Objectives

**Primary:**

To identify the acceptability and feasibility of recruiting people with thoracic cancer to a trial of a short-term rehabilitation service over a twelve-month period.

**Secondary:**

1. To identify acceptability and feasibility of delivering the short-term rehabilitation service over 1-3 contacts over 30 days
2. To evaluate performance of selected clinical outcome measures
3. To obtain recruitment rate to estimate sample size for a full trial
4. To evaluate trial procedures
5. To evaluate fidelity of service delivery and uptake of discrete service components
6. To describe pattern of ongoing referrals to local rehabilitation services
7. To identify and describe use of other health care resources during trial period

# 5 Trial design

This study is assessing the feasibility of conducting a parallel group 1:1 randomised controlled multi-centre trial to test a short-term integrated rehabilitation service for people recently diagnosed with thoracic cancer (lung cancer or MPM). To assess the feasibility of trial processes including recruitment, attrition, service components and mode of delivery in this population and setting, and in order to obtain an estimate of parameters of the service to inform the design of the large-scale trial, a feasibility randomised controlled trial is deemed necessary.(64, 65) It will determine if patients with thoracic cancer are willing to be randomised to receive the service or usual care and the willingness of clinicians providing their care to refer them. A randomised controlled design is

considered to be optimal to minimise bias and to estimate the benefit of an intervention. If feasibility is demonstrated in this trial, the design will be used in a future powered randomised controlled trial to estimate the benefit of the rehabilitation service.

Participants will be randomised to receive the short-term integrated rehabilitation service and NHS standard care or to receive standard NHS care over 30 days (figure1). Follow up measures, will be collected at 30 days and 60 days for all patient participants. All patients participating in the trial will have the same access to specialist medical and nursing services as was available to them prior to entering the trial.

## 5.1 Outcomes

As this is a feasibility trial we do not have a primary outcome. The outcomes relate to feasibility parameters, including recruitment and retention rates, completion of outcome measures, successful outcome assessment blinding, treatment fidelity, and contamination. Bespoke questions to elicit experiences of participating in the trial will be included in the questionnaire booklet at 60 days. Answering these feasibility questions will establish if a large-scale randomised controlled trial can be performed in the period following diagnosis. A 60-day follow-up period has been chosen in order to provide sufficient data on recruitment and retention for a large-scale trial.

If feasibility is demonstrated, then the service can be tested in a full randomised single blind trial in this setting. The recruitment rate will be used to determine the sample size of the full trial. It will inform future studies of rehabilitation interventions in patients with thoracic cancer. If effective, this model of care could benefit other cancer patients and their families, as well as others with chronic conditions.

Outcomes:

1. Proportion of eligible participants randomised
2. Proportion of randomised patients remaining on trial for 30 days for 1, 2 and 3 contacts; reasons for drop out
3. Recruitment rate
4. Response and completion rates to outcome measure questionnaires & reasons for missing data.
   a. Integrated Palliative Care Outcome Scale
   b. Physical Activity Scale for the Elderly (PASE)
   c. Self-Efficacy Scale Chronic Disease
   d. Functional Assessment of Cancer Therapy -Lung Trial Outcome Index (TOI)
   e. Client Services Receipt Inventory
   f. EQ-5D-5L
   g. Patient experience of trial participation

5. Intervention fidelity:
   a. number of planned contacts per participant, mode of contact, proportion of participants with a rehabilitation plan
   b. proportion of patients & carers receiving support to:
      i. self-manage symptoms
      ii. maintain physical activity and fitness
      iii. maintain task performance and participation in activities
      iv. referrals to other services
6. Frequency and type of discrete Behaviour Change Techniques used during intervention (66) used during intervention delivery

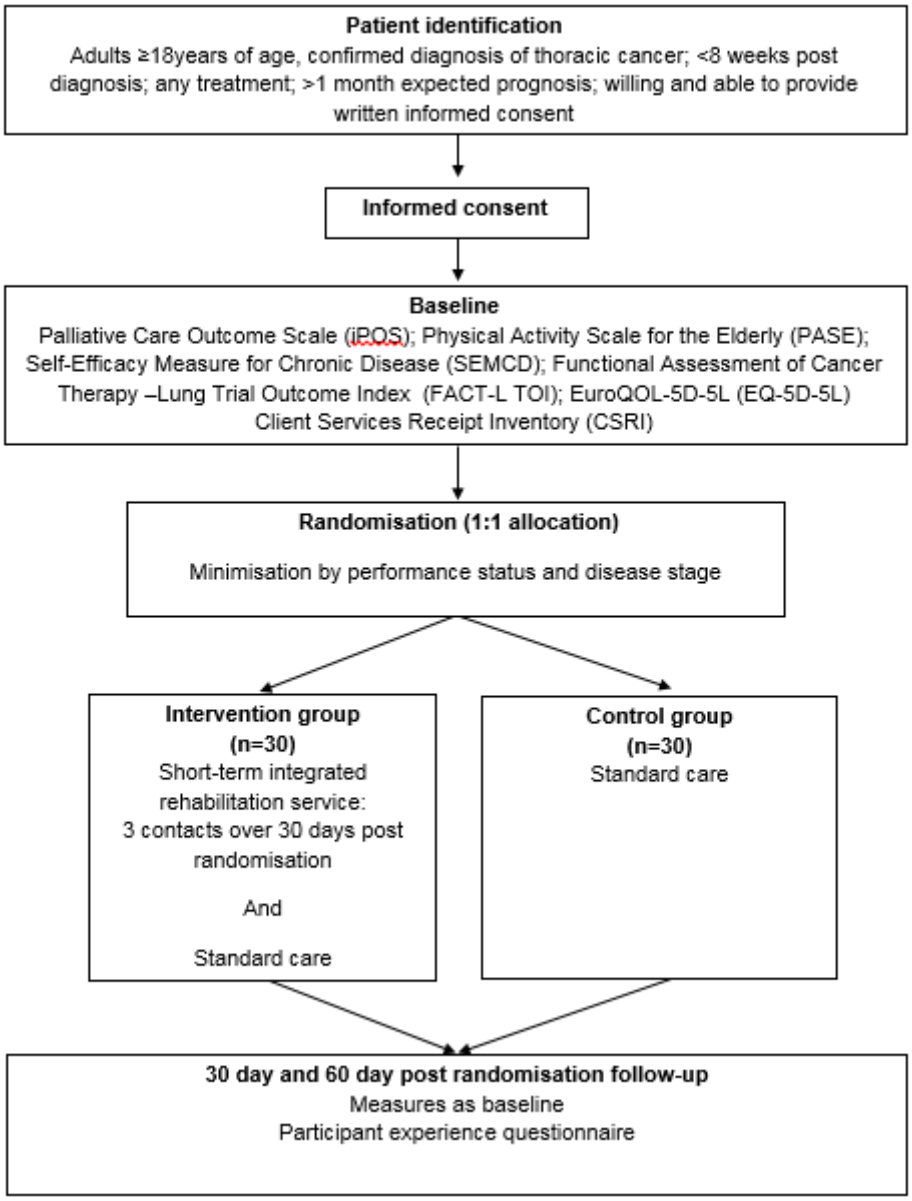


FIGURE 1 FEASIBILITY TRIAL FLOW DIAGRAM

# 6 Selection of Participants

## 6.1 Inclusion criteria

- Age ≥18 years
- Clinical or histological diagnosis of thoracic cancer; NSCLC, SCLC or MPM, within the last 8 weeks
- ECOG performance status 0-3 or AKPS
- Ability to respond to questions in written English – or availability of interpreters to enable this
- Willing and able to provide written informed consent.

## 6.2 Exclusion criteria

- Co-existing progressive neurological condition (e.g. multiple sclerosis, motor neurone disease)
- ECOG performance status 4 (due to association with short survival)
- Inability to complete patient questionnaires due to cognitive impairment, or language difficulties and lack of interpreters
- Patients currently receiving specialist rehabilitation, or planned to receive within the next month.
- Receiving palliative care with expectation of death within 1 month
- Concurrent and/or recent involvement in other research that is likely to interfere with the intervention during period of study enrolment

## 6.3 Recruitment

Patients will be recruited from three trial sites, with trial coordination and data collection performed by the Chief Investigator, Jo Bayly. Participants may be identified from within the trial sites by out-patient or in-patient services. We anticipate that most patients will be recruited from respiratory and oncology services by physicians, lung cancer nurse specialists and clinical research nurses. However, we expect a small number of participants will be recruited from other in-patient and out-patient services, including gerontology, acute medicine, surgery and palliative care.

**Awareness raising:**

- Some weeks before the trial opens at each site we will arrange meetings at each site, e.g. lunch time workshops for clinicians and PPI representatives. The session will include information about the trial, why it is being conducted, the eligibility criteria and equipoise.
- We will train local clinicians and research nurses how to identify eligible patients, refer and recruit patients and how to complete the study screening log.
- We will develop study posters and flyers detailing the trial to be used by referring clinicians and for display in appropriate setting within each site and via patient information centres, primary care centres and support groups.

**Participant recruitment at a site will only commence when the trial has:**

- Been confirmed by the Sponsor (or its delegated representative)
- Received HRA Approval, and
- Has confirmed Capacity and Capability

### 6.3.1 Patient screening, initial approach & information:

Patients diagnosed with NSCLC, SCLC or MPM will be approached by a member of their usual health care team or a research nurse and screened against the eligibility criteria for trial entry. The research nurses and clinicians involved in screening will be supplied with a brief study summary prompt sheet to facilitate identification of participants in busy clinical settings.

The clinician or research nurse will give written information to eligible patients about the study. The right of a patient to refuse participation without giving reasons will be respected. However, as this is a feasibility trial, participating sites will complete screening logs of all patients screened for entry into the trial who do not go onto be randomised and will include reasons for ineligibility or declining participation when offered by the patient. This

information will be collected from sites on a regular basis and monitored by the Trial Management Group.

If the patient is interested and agrees for their detail to be sent to the researcher to learn more about the study, the clinician or research nurse will complete a standard referral from to check that patients meet the eligibility criteria and send this to the researcher.

### 6.3.2 Participant recruitment:

The researcher or research nurse will then contact the patient by telephone to explain the study, send out the study participation sheet and arrange a face to face visit after a minimum of 24 hours. This visit will usually be arranged at the participant's next convenient scheduled hospital appointment; however, it can take place at their home or anywhere else the participant feels would suit them (such as a relative's home). During the visit the researcher or research nurse will answer any questions. If the patient is willing to enter the study, the researcher or research nurse will take the participant through the consent process and administer the baseline questionnaire. A member of the participant's family and/or a carer may accompany the patient during the recruitment process.

# 7 Informed consent

It is the responsibility of the Chief Investigator, or a clinical research nurse delegated by the Chief Investigator to obtain written informed consent from each participant prior to participation in the trial, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the trial.

The person taking consent will be suitably qualified and experienced, and will have been delegated this duty by the CI/ PI on the Delegation Log.

Adequate time must be given for consideration by the participant before taking part. Consent will be sought at least 24 hours after being given the study documentation. If the potential participant wishes to waive this period, the researcher will record the participants stated reason in the medical notes (including version and date of the PIS) when the participant information sheet (PIS) has been given to the participant. The Investigator or designee will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason.

No trial procedures will be conducted prior to the participant giving consent by signing the Consent form. Consent will not denote enrolment into trial. A copy of the signed Informed Consent form will be given to the participant. The original signed form will be retained in the trial file at site and a copy placed in the medical notes. The PIS and consent form will be reviewed and updated if necessary throughout the trial (e.g. where new safety information becomes available) and participants will be re-consented as appropriate.

# 8 Intervention

**Short Term Integrated Rehabilitation for Thoracic Cancer- Conceptual Framework**

The conceptual framework (figure 2) of the short term integrated rehabilitation service builds on the 'Holistic Biopsychosocial Model of Illness' and the 'Rehabilitation Processes' described by Wade, (67,

68) the 'Features of Illness' described by Toombs(69) and the behaviour change framework 'The Behaviour Change Wheel', developed by Michie et al.(66)

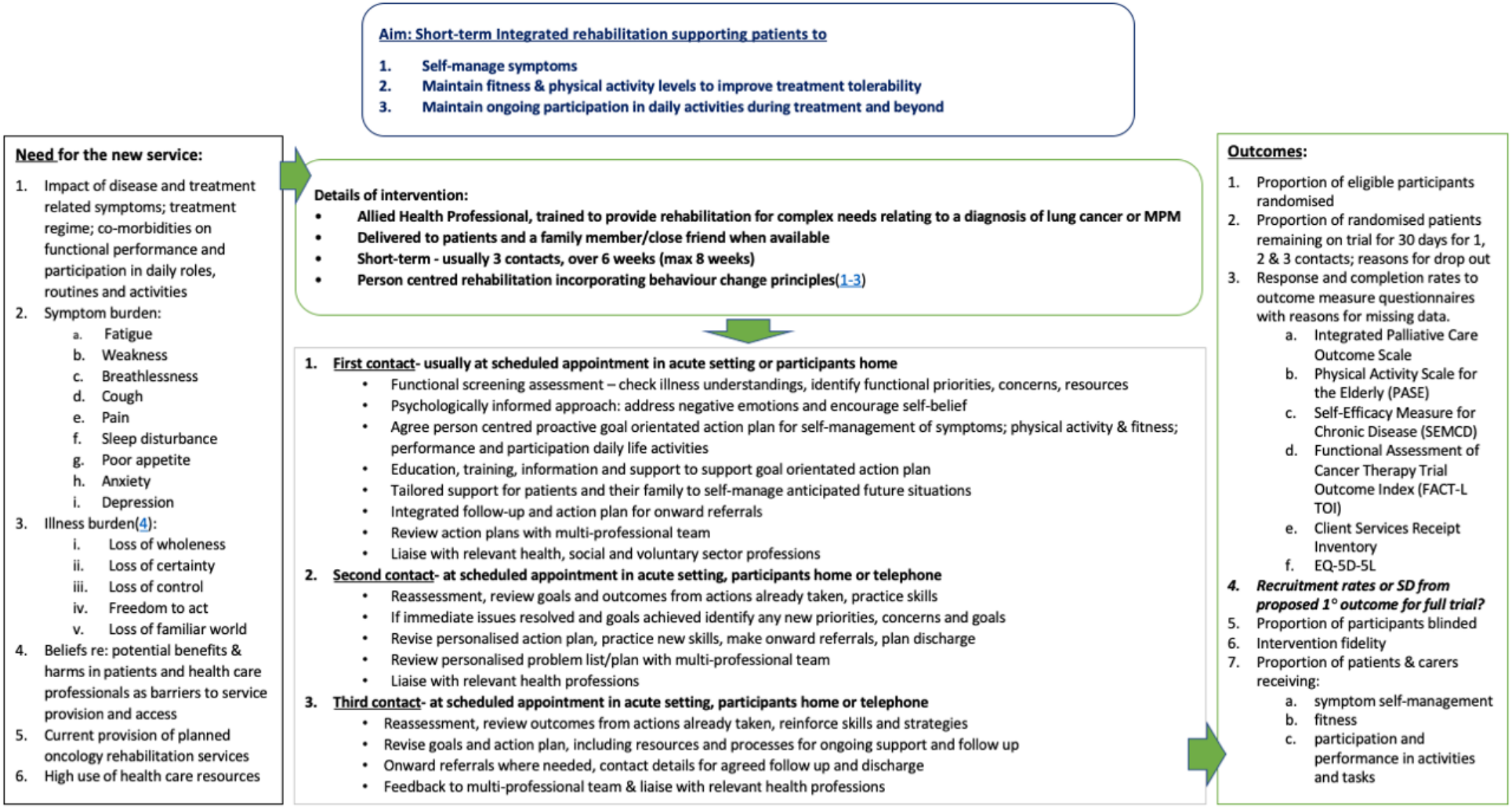


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FIGURE 2 CONCEPTUAL FRAMEWORK FOR INTERVENTION

# 10 Trial procedures

## 10.1 Randomisation Procedures

Following participant consent, and confirmation of eligibility the registration/randomisation procedure described below will be carried out.

**Timing of Randomisation**

Informed consent for entry into the trial must be obtained and baseline assessments performed prior to randomisation. Following confirmation of written informed consent and eligibility, participants will be randomised into the trial by an authorised member of staff at the trial site. Randomisation will be performed centrally using the independent web-based system at the UKCRC Registered Clinical Trials Unit at King's College London CTRU randomisation system (office hours, 9:00-17:00) and should take place as soon as possible after consent is obtained and eligibility confirmed.

**Treatment Allocation:** Participants will be randomised at the individual level with a 1:1 allocation. Minimisation will ensure groups are matched for ECOG performance status (0-1/2-3) and disease stage (I-II/III-IV) as these factors mediate symptom burden and physical function. A proportion will be entered initially using simple randomisation to create a level of initial imbalance and a minimisation algorithm will maintain a level of randomness to preserve pre-randomisation allocation concealment. Once randomised, the system will automatically generate a full audit trail of the process and send emails to relevant investigators in a blinded or un-blinded format, depending on their role. Follow-up outcomes will be assessed by postal questionnaires handled by an independent staff kept blind to participants' treatment allocation. Two data entry systems will be created to maintain blinding, the first used for outcome assessments and the second by the student for data regarding compliance with the intervention and safety.

Participants are considered to be enrolled into the trial following: consent, confirmation of eligibility, completion of the registration/randomisation process, allocation of the participant trial number and intervention.

## 10.2 Intervention procedures

### 10.2.1 Intervention arm:

**Intervention delivery**

The intervention will be offered following procedures outlined in a Standard Operating Manual using agreed standard clinical records. The intervention is designed to integrate with the care the participant receives from usual health care team at each site. Details of contacts will be communicated routinely to oncology, the Lung CNS and primary care. Components will be delivered over (up to) three contacts with an AHP usually over 6 weeks (30 working days). To avoid excessive clinic visits, the AHP will try to see patients at their regular scheduled hospital outpatient appointments, treatment or investigations. A member of the participant's family and/or a carer may accompany the patient during the intervention. The first contact will be face-to-face in the hospital setting and will involve assessment, identification of concerns and goals and an agreed individualised action plan. Intervention content and structure will be tailored to the individual. A member of the research team will contact the clinical care team to confirm that the patient is well enough to be contacted prior to the next study visit. Subsequent contacts, depending on patient preference, can take place at scheduled hospital appointments, the patient's home and may use telephone services. The action plan will be reviewed at the second and third appointments where the participants will be given the opportunity to practice any strategies taught and to raise new concerns. After the third appointment participants will be signposted to community resources to support their on-going self-management. If any issues remain outstanding which require follow up from a health care professional, the participant will be referred to existing local generic rehabilitation services or to the most appropriate member of their health care team.
The AHP has completed oncology and palliative care training in this specialty. Prior training includes disease trajectories, symptoms and concerns, advanced communication skills and interventions to manage common symptoms including pain, breathlessness and fatigue.

**Key Intervention Components**

1. Functional screening and assessment (including checking illness understandings, limiting symptoms, current and pre-illness activity levels, current performance in daily activities, avoidance behaviours, priorities, concerns, beliefs around activity)
2. Psychologically informed approach to address fears, negative emotions and encourage self-belief (i.e. motivational interviewing)
3. Agree goals to work towards that address the person's concerns, symptoms and priorities
4. Agree a proactive goal orientated action plan to support:
    a. self-management of symptoms
    b. physical activity and fitness
    c. functional performance and participation in daily life activities, roles and routines

    *(Person may prioritise goals in any or all of a-c)*
5. Education, training, information and support to support goal orientated action plan- to include some or all of:
    a. information about potential consequences of each action plan item (e.g. use of breathing recovery techniques improves management of breathlessness episodes with consequent relief of associated distress and fear; strategies to minimise sedentary time and promote habitual physical activity and exercise with consequent improvements in task performance and reduction in fatigue; use of walking aid to relieve breathlessness, compensate for weakness and therefore to maintain independent mobility)
    b. demonstration and practise of skills
    c. implementation intention plans
    d. habit promotion, prompts & cues

e. identifying supportive resources within person and their family
f. written and multi-media resources
g. provision of walking aids and hand held fans when indicated
h. information about self-monitoring, how to recognise and manage signs and changing symptoms,

6. Tailored action planning for patients and their family to self-manage anticipated future situations, e.g. deterioration or new symptoms. This will include information about self-help resources; when, how and who to contact to access medical and/or rehabilitation services relating to changes in functional performance or symptoms in their locality.
7. Integrated follow-up and action plan for onward referrals (including sign-posting or referral to existing local rehabilitation and community support services)
8. Review action plans with multi-professional team & liaise with relevant health, social and voluntary sector professions

### 10.2.2 Control arm:

Standard care is the treatment and care provided routinely for people with lung cancer or MPM. It includes appointments with oncologists and other physicians and oncology or other medical treatments. It includes appointments with Lung Cancer Nurse Specialists and appointments with other members of the health care team, including GP, palliative care doctors and nurses or social workers. The Lung Cancer Nurse Specialist at each of the three hospital sites commences contact with a patient with lung cancer ideally when there is a suspicion of lung cancer, continuing at key points throughout the whole of the patient pathway, through diagnosis, treatment, follow-up, palliative and end of life care. Contacts with the Lung CNS are permitted in both trial arms and will be captured as part of baseline and follow up assessments (CSRI).

## 10.3 Subsequent assessments and procedures

The schedule of all trial assessments and interventions is summarised in Appendix 1.

**Screening Data**

Potential participants approached but not going on to be randomised will be included on the screening log. Anonymised information for these patients will be collected including:

- Disease histology and stage
- Identification setting (i.e. out-patient clinic, in-patients, community
- Method of initial approach
- Date screened
- Approached/not approached for trial with reason for non-randomisation (not eligible; eligible but declined & reason if appropriate; other reason for non-randomisation)

This information will be collected on a monthly basis from each trial site. Documented reasons for ineligibility or declining participation with be closely monitored by Trial Management Group. Screening data forms a crucial measure of this feasibility study therefore it is essential that this information is collected as outlined.

**Eligibility Assessments**

The following assessments need to be performed to assess eligibility (see section 6 above for full eligibility criteria) prior to randomisation.

- Review of medical notes to establish clinical or histological diagnosis of NSCLC, SCLC or MPM diagnosed within last 8 weeks and co-morbid conditions
- Eastern Oncology Performance Status 0-3

**Baseline Assessments and Data Collection (pre-randomisation)**

Following written consent and prior to randomisation the participant will be assessed by a member of the research team either at the trial site or, if the participant prefers, at the participant's home. The following baseline assessments will be carried out:

**Assessments to be performed by the research team (**collected to inform analysis of feasibility outcomes, recruitment & dropout rates (acceptability of intervention and acceptability of randomisation and trial procedures) **:**

- Medical review- to obtain information on diagnosis, history, comorbid conditions and general health
- Demographic data- to obtain data on age, gender, ethnicity, education, living circumstances.
- ECOG
- Planned oncology/palliative care treatment
- Oncology/palliative care treatment received

**Participant Reported questionnaires** (collected to evaluate feasibility of outcome measures to capture change in participant's health status, completion rates**,** missing data)**:**

- Integrated Palliative Outcome Scale (iPOS)- assesses symptoms, information needs, participant's perception of family anxiety, provides space for free text concerns, 1 week recall. Scores range from 0 (not a problem) – 4 (overwhelming). Symptoms scoring 3-4 will be documented on the case report form to ensure these are known to the AHP delivering the rehabilitation service.

- Physical Activity Scale for the Elderly (PASE) - validated in people with lung cancer, assesses self-reported physical activity levels, 1 week recall.
- Self-Efficacy Measure Chronic Disease (SEMCD) - assesses self-beliefs to cope with impact of disease.
- Functional Assessment of Cancer Therapy- Lung Trial Outcome Index (FACT-TOI)- assesses functional and physical well-being and specific lung cancer related concerns
- EQ-5D-5L- measures health related quality of life and enables economic evaluation in QALYs
- Client Services Receipt Inventory (CSRI)- provides a measure of participants use of other health and social care resources

**1st Contact (within 7 days of baseline, may be at same time as baseline) - face to face**

Functional screening & assessment

**2nd Contact (within 2 weeks of 1st contact) - face to face or telephone**

Functional screening and review of goals and action plan

**3rd Contact (within 2 weeks of 2nd contact) - face to face or telephone**

Functional screening and review of goals and action plan

Onward referrals & signposting

Number of completed contacts

Reasons for drop out

Components of service used (a. symptom self-management b. physical activity/fitness; c. task performance/participation)

**30 & 60 days' post randomisation (by postal questionnaire)**

**Participant Reported questionnaires:**

- Integrated Palliative Outcome Scale (iPOS)
- Physical Activity Scale for the Elderly (PASE)
- Self-Efficacy Measure Chronic Disease (SEMCD) - assesses self-beliefs to cope with impact of disease
- Functional Assessment of Cancer Therapy- Lung Trial Outcome Index (FACT-TOI)
- EQ-5D-5L
- Client Services Receipt Inventory (CSRI)
- Participant experience (at 30 days- FACIT-TS-PS and bespoke questions)

**A schedule of all trial assessments and procedures is set-out in Appendix 1.**

### 10.4 Discontinuation/withdrawal of participants

In consenting to participate in the trial, participants are consenting to intervention, assessments, follow-up and data collection.

A participant may be withdrawn from trial whenever continued participation is no longer in the participant's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing the trial may include:

- disease progression becoming too unwell to participate in rehabilitation
- intercurent illness becoming too unwell to participate in rehabilitation
- patients withdrawing consent
- persistent non-compliance to protocol requirements

The decision to withdraw a participant from treatment will be recorded in the CRF and medical notes. If a participant explicitly states they do not wish to contribute further data to the trial their decision must be respected and recorded in the CRF and medical notes.

### 10.5 Stopping Rules

- If the sponsor or the TMG raise any new safety or ethical concerns over the trial processes and make final recommendations to discontinue the trial
- To assist the work of the TMG, we will monitor the number of deaths, emergency attendances, hospital admissions and length of hospital stay in each arm in total and by disease. Any noticeable increase in these parameters will be subject to full investigation and will be acted upon. They will be reported bi-monthly to the TMG.
- If the study is discontinued prematurely, active participants will be informed and no further participant data will be collected.

### 10.6 Definition of End of Trial

The expected duration of the trial is 1 year from consent of the first participant or the date of the last visit/ telephone follow up/home visit of the 60th participant, whichever occurs first.

## 11 Safety Reporting

This is a very low risk study. Rehabilitation is tolerated by people with a wide range of health conditions. We do not anticipate any adverse events relating to the intervention.

### 11.1 Adverse Events

| Term | Definition |
|---|---|
| Adverse Event (AE) | Any untoward medical occurrence in a patient or trial participant, which does not necessarily have a causal relationship with the intervention involved. |
| Serious Adverse Event (SAE). | Any adverse event that:<br>• results in death,<br>• is life-threatening*,<br>• requires hospitalisation or prolongation of existing hospitalisation**,<br>• results in persistent or significant disability or incapacity, or<br>• consists of a congenital anomaly or birth defect. |

| | |
|---|---|
| | Medical judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious. |
| * A life- threatening event, this 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.<br>** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE. | |

## 11.2 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

### 11.2.1 Severity

The generic categories below are given for use as a guide.

| Category | Definition |
|---|---|
| Mild | The adverse event does not interfere with the participant's daily routine, and does not require further intervention; it causes slight discomfort |
| Moderate | The adverse event interferes with some aspects of the participant's routine, or requires further intervention, but is not damaging to health; it causes moderate discomfort |
| Severe | The adverse event results in alteration, discomfort or disability which is clearly damaging to health |

### 11.2.2 Causality

The assessment of relationship of adverse events to the intervention is a clinical decision based on all available information at the time of the completion of the case report form.

The following categories will be used to define the causality of the adverse event:

| Category | Definition |
|---|---|
| *Definitely:* | There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. |
| *Probably:* | There is evidence to suggest a causal relationship, and the influence of other factors is unlikely |
| *Possibly* | There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events). |
| *Unlikely* | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial |

| | |
|---|---|
| | intervention). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatments). |
| *Not related* | There is no evidence of any causal relationship. |
| *Not Assessable* | Unable to assess on information available. |

### 11.2.3 Expectedness

| Category | Definition |
|---|---|
| *Expected* | An adverse event which is consistent with the information about the intervention listed in this protocol- Section 10.3 |
| *Unexpected* | An adverse event which is not consistent with the information about the intervention listed in this protocol- Section 10.1* |

* This includes listed adverse events that are more frequently reported or more severe than previously reported.

The reference document to be used to assess expectedness of serious adverse events against the Intervention is in Section 10.3 of this Protocol.

**The events listed below describe expected procedural/disease related AEs:**

- Chemotherapy, radiotherapy and surgical side-effects
- Expected deterioration related to underlying cancer diagnosis
- Expected deterioration related to underlying co-morbidity
- Expected symptoms relating to underlying cancer or co-morbid condition, including pain, breathlessness, fatigue, nausea, vomiting, insomnia, anorexia, anxiety, depression and confusion

## 11.3 Serious Adverse Events that do not require reporting

**Expected procedural and or disease related events not to be classified as SAEs for expedited reporting within this trial.**

**Hospitalisation or admission to hospice or nursing home due to:**

- Care-giver burden
- Expected deterioration related to underlying cancer diagnosis
- Expected deterioration related to underlying co-morbidity
- Treatment which was elective or pre-panned, for a pre-existing condition which does not lead to further complications.
- Any admission to hospital or other institution when there was no deterioration in condition.

These events will continue to be recorded in the medical records, CRF and the AE log.

## 11.4 Procedures for recording and reporting Adverse Events and Serious Adverse Events

All adverse events will be recorded in the medical records. They will also be recorded, with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate in the CRF.

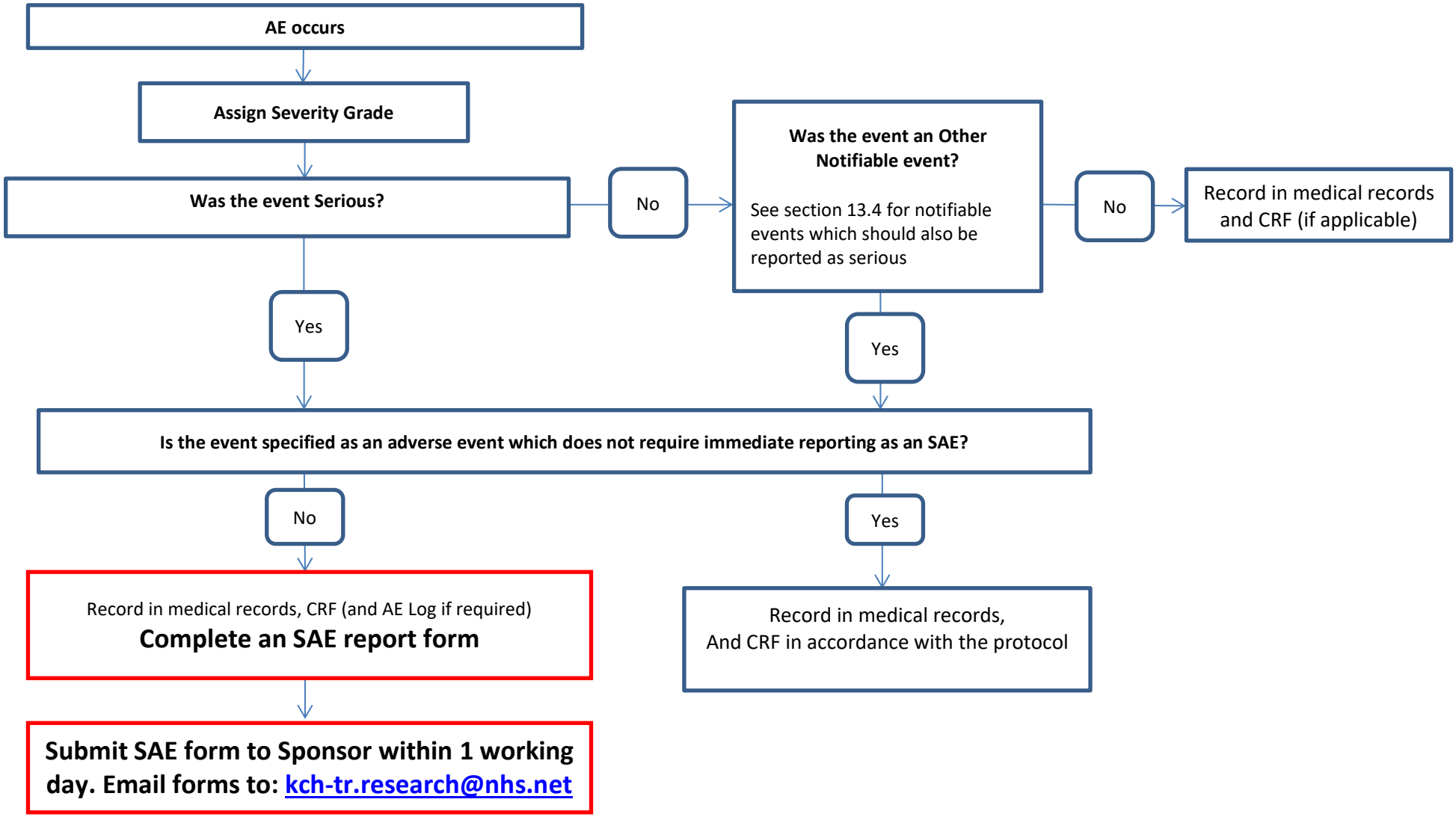
All serious adverse events will be recorded in the medical records (CI or research nurse) and the CRF (CI), All adverse events and serious adverse events from all sites will be recorded in the sponsor's AE log (CI). The sponsors AE log is used to collate SAEs and AEs so that the CI can review all in one place for trend analysis. The AE log of SAEs will be reported to the sponsor at least once or twice per year.

All SAEs (except those specified in section 10.3 as not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete the sponsor's SAE form and the form will be preferably emailed to the Sponsor within 1 working day of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.
Where the event is unexpected and thought to be related to the intervention, this must be reported by the Chief Investigator / Sponsor to the Health Research Authority within 15 days.

Completed SAE forms must be sent within 1 working day of becoming aware of the event to the Sponsor
**Email forms to: kch.tr-research@nhs.net**

SAEs will be reported to the sponsor until 30 days following last interventional procedure.
Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary.
Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to the Sponsor as further information becomes available.

**Flow Chart for SAE reporting (this simple flow chart is for a single site trial, please amend in line with trial specific requirements)**



## 11.5 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

## 11.6 Notification of reportable protocol violations

A reportable protocol violation is a breach which is likely to effect to a significant degree:
(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial.
The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

## 11.7 Trust Incidents and Near Misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.
b. It is contrary to specified or expected standard of patient care or service.
c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d. It puts the Trust in an adverse position with potential loss of reputation.
e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.
A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

## 11.8 Distress Protocol

If patients or family members become upset during the consent or intervention meetings, the researcher will first offer to pause, postpone or stop the meeting or intervention and advise again that participation is voluntary. In the case of severe distress, the participant will be encouraged to share his or her feelings with a member of their health care team. The researcher will offer to contact their health care team on their behalf. We anticipate that distress caused by the research will be infrequent and is likely to reflect the presence of advanced disease and not the research processes.

If participants disclose ideation of self-harm or other risk to themselves or others, then this will be dealt with as an urgent matter and clinical help will be sought, if possible in agreement with the participant. However, if the research team believes the participant to be at imminent risk and refuses to allow voluntary disclosure to the clinical team, the research team will breach

confidentiality. Based on our experience with other studies, we anticipate that this will be an extremely rare occurrence. Provision will be made to ensure researchers have PI or senior back up available by phone whenever they are undertaking data collection.

# 12 Data management

## 12.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998.
The Case Report Forms (CRFs) will not bear the participant's name or other personal identifiable data. The participant's initials, date of birth and trial identification number, will be used for identification and this will be clearly explained to the patient in the Patient information sheet. Patient consent for this will be sought.

## 12.2 Data collection tools and source document identification

Data will be collected from sites on trial specific case report forms (CRFs)
Source data, including assessment findings, treatment delivered and treatment plan, will be recorded in the medical case sheet and will be accurately transcribed on to the CRF.

Telephone contacts, including reminder contacts for appointments or prompts to return questionnaires) will also be recorded in the medical case notes and accurately transcribed to the CRF. It is the responsibility of the chief investigator to ensure the accuracy of all data entered in the CRFs. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

## 12.3 Completing Case Report Forms

CRFs will usually be completed by the CI. CRFs must be completed and signed by staff that are listed on the delegation log and authorised by the CI/ PI to perform this duty. The CI/PI is responsible for the accuracy of all data reported in the CRF.
Once completed the original CRFs must be sent to Jo Bayly, Cicely Saunders Institute, King's College London, SE5 9PJ, and a copy kept at site. The CRFs must be returned within 1 week of the final participant contact. Source data verification of a CRF page will be completed and reported on the form so all data queries are answered prior to submission where possible.

## 12.4 Data handling

In the study, patient data as described in section 12 above, will be collected from patients in accordance with the patient consent form, patient information sheet and sections 12 and 14 of this protocol. The Participant Case Report Forms and the baseline and follow up participant reported questionnaire booklets will be sent to Jo Bayly and Dr Gao Wei for statistical analysis. KCH/KCL, as the study sponsor, will act as the data controller of such data for the study.

Jo Bayly, Cicely Saunders Institute, King's College London, SE5 9PJ, will process, store and dispose of Participant Case Report Forms and participant questionnaire booklets in accordance with all applicable legal and regulatory requirements, including the Data Protection Act 1998 and any amendments thereto. Participant data will be stored centrally in a locked filing cabinet controlled by the Chief Investigator. Anonymised participant data will be entered onto a secure password

protected database held at the Cicely Saunders Institute in accordance with the 1998 Data Protection Act.

The Participant Case Report Forms and the baseline and follow up participant reported questionnaire booklets will not be transferred to any party not identified in this protocol and are not to be processed and/or transferred other than in accordance with the patients' consent.

# 13 Statistical Considerations

## 13.1 Feasibility outcome(s)

As this is a feasibility study there is no primary outcome.

Outcomes will evaluate feasibility parameters including the acceptability of the trial processes, outcome measures and the rehabilitation service components and processes. Data will be summarised overall and by trial arm with corresponding 95% confidence intervals for the following feasibility outcomes.

1. Proportion of eligible participants randomised

2. Proportion of randomised patients remaining on trial for 30 days for 1, 2 and 3 contacts; reasons for drop out

3. Response and completion rates to outcome measure questionnaires with reasons for missing data.
   a. Integrated Palliative Care Outcome Scale
   b. Physical Activity Scale for the Elderly (PASE)
   c. Self-Efficacy Measure for Chronic Disease (SEMCD)
   d. FACT-L & Trial Outcome Index (TOI)
   e. Client Services Receipt Inventory
   f. EQ-5D-5L
   g. FACIT-TS-PS

4. Recruitment rates

5. Intervention fidelity:
   a. number of planned contacts per participant, mode of contact, proportion of participants with a rehabilitation plan
   b. proportion of patients & carers receiving support to:
      i. self-manage symptoms
      ii. maintain physical activity and fitness
      iii. maintain task performance and participation in activities

## 13.2 Sample size calculation

As this trial is designed to assess the feasibility of conducting an effectiveness trial, a formal power calculation is not appropriate. To determine feasibility of recruitment and inform future work, Browne et al. state that at least 30 patients should be included to estimate a parameter for sample size calculation.(70) As the trial is randomized, and rates of uptake, adherence and attrition will be examined as part of this trial, a total of 60 patients are required.

## 13.3 Planned recruitment rate

We are recruiting from three sites over one year. In 2015, 1,238 new cases of lung cancer and approximately 310 new cases of malignant pleural MPM were diagnosed across the three sites(71) This equates to 129 new cases per month). Therefore, we expect to be able to recruit 60 participants across the 12-month recruiting period (5 participants per month).

## 13.4 Randomisation methods

- Individual 1:1 parallel randomisation
- minimisation
- minimisation variables: AKPS/ECOG performance status (0-1/2-3); disease stage (I-II/III-IV)
- equal allocation between treatment arms
- random allocation lists and the minimisation programme will be generated by the CTRU at King's College London.

## 13.5 Statistical analysis

### 13.5.1 Summary of baseline data and flow of participants

Baseline characteristics of the intervention and usual care arms will be summarised using descriptive statistics. Participant flow through the trial will be reported in a consort flow diagram (http://www.consort-statement.org/).

### 13.5.2 Feasibility analysis

A single analysis will be completed once available follow up data from 60 participants have been recorded. The statistical analyses of the feasibility outcomes include:

- The proportion of eligible patients randomised (feasibility criteria =30%)
- The proportion of patients who remain in study for 30 and 60 days (feasibility criteria = 50%)
- The proportion of missing data will be summarised overall and for each trial outcome, at each time point of assessment
- Where available, reasons for missing data will be provided (72)
- Proportion of patients for whom patient reported outcome measurement blinding is maintained
- Treatment fidelity and contamination will be summarised by the number of patient contacts, mode of contact and the proportion of patients with a rehabilitation plan, by treatment arm
- In keeping with the feasibility design, clinical outcome data will be summarised descriptively with no formal statistical testing for superiority of the interventions compared to usual care

# 14 Record keeping and archiving

At the end of the trial, all essential documentation will be archived securely by the CI at the Cicely Saunders Institute for a minimum of 5 years from the declaration of end of trial. Trial data held by the King's College CRTU will be archived in the King's college archive facility. Site data and documents will be archived at participating sites in accordance with local R&D governance requirements.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with all applicable regulatory requirements.
The sponsor will notify sites when trial documentation can be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

# 15 Oversight Committees

## 15.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator and trial staff, two PPI representatives and a representative from the study sponsor and lead R&D department. The TMG will be responsible for overseeing the trial, including data & safety monitoring. The group will meet regularly bi-monthly and will send updates to PIs.
The TMG will review recruitment figures, SAEs and substantial amendments to the protocol prior to submission to the REC. All PIs will be kept informed of substantial amendments through their nominated responsible individuals (if applicable, multisite trials).

# 16 Ethical requirements and patient and public involvement

## 16.1 Ethics and Health Research Authority (HRA)

The sponsor will ensure that the trial protocol, participant information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate research ethics committee and HRA, prior to any participant recruitment. The protocol, all other supporting documents including and agreed amendments, will be documented and submitted for ethical and regulatory approval as required. Amendments will not be implemented prior to receipt of the required approval(s).
Before any NHS site may be opened to recruit participants, the Chief Investigator/Principal Investigator or designee must ensure confirmation of Capacity and Capability has been given by the local R&D office. It is the responsibility of the CI/ PI or designee at each site to ensure that all subsequent amendments gain the necessary approvals. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual participants (see section 13.5 for reporting urgent safety measures).
An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The chief investigator will prepare the APR.
Within 90 days after the end of the trial, the CI/Sponsor will ensure that the main REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.
The CI will supply the Sponsor with a summary report of the trial, which will then be submitted to the REC within 1 year after the end of the trial.

## 16.2 Patient and public involvement (PPI)

The Cicely Saunders Institute PPI Group - a group set up and organised by service users, clinical and research staff – meet on a monthly basis, and provides PPI support to the Institute's research.
Members undergo formal PPI training provided by the local NIHR CLAHRC. The preliminary research design and service components emerged from discussion with members.

The funding application for the trial was informed by patients participating in another study of people with lung cancer (led by one of the supervisors, Dr Maddocks), who thought it could compliment and fill gaps within current rehabilitation services they were being offered. In addition, two PPI representatives from the National Cancer Research Institute, Supportive and Palliative Care Clinical Studies Group have offered peer review. Their suggestions have been incorporated into the study design, for example, the language used to describe rehabilitation and its aims,and the restriction to short PROMs. Following the funding award, the overall study design was presented and discussed at two Public Involvement Workshops held in November 2016 and April 2017 at the CSI. They confirmed that the service has the potential to fill gaps in care provision and the importance of providing clear information in public facing materials regarding the aims and scope of the rehabilitation service being tested in this trial.
The Feasibility Trial Study Poster & Participation Information Leaflets and Consent Form have been developed with the involvement of members from the CSI Public Involvement Online Forum. A member of the CSI Public and Patient Involvement Forum has agreed to join the Trial Management Group. A second PPI representative will be invited from the CSI forum or from the PPI groups of the participating sites. Dissemination of the trial findings will be supported by members of the CSI & GSTT PPI groups and the South London CLARHC. The Chief Investigator has also engaged with National Patient Support Groups for Lung Cancer and MPM. Both groups have expressed that they will be keen to support dissemination of the trial findings.

# 17 Monitoring

The chief investigator is the data custodian and is responsible for monitoring the conduct of the trial. The degree of monitoring will be proportionate to the risks associated with the trial and will include checking completion of screening and recruitment logs, recording of approach and consent processes in medical case notes, completion of Case Report Forms against source data and adverse event reporting. A trial specific oversight and monitoring plan will be established for studies by the Trial Management Group. The trial will be monitored in accordance with the agreed plan.

# 18 Finance

The study is funded through a HEE/NIHR Clinical Doctoral Research Fellowship Award. This award covers the salary costs of the CI and all other research costs associated with running the feasibility trial.
Neither the PI nor other Trial Management Group members have any financial interests in the conduct of the trial.

# 19 Insurance

KCL/KCH Joint Sponsors
King's College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that KCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. King's College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

KCH will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance

undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&I Office. The Trust cannot accept liability for any activity that has not been properly registered and Trust approved. Potential claims should be reported immediately to the KCH R & I Office.

## 20 Publication policy

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines prior to the start of recruitment.
The success of the trial depends on the collaboration of all participants. For this reason, credit for the main results will be given to those who have collaborated in the trial, through authorship and contribution. Uniform requirements for authorship credit will be based only on contribution to:

- Conception and design, or acquisition of data, or analysis and interpretation of data,
- Drafting the article or revising it critically for important intellectual content.
- Final approval of the version to published
- All these conditions are met (www.icmje.org).

Therefore, the CI, key clinical advisors and relevant CTRU staff will be named as authors in any publication. In addition, collaborators will be listed as contributors for the main trial publication. We will give details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of feasibility, either for trial publication or oral presentation purposes without the prior permission of the TSC. In addition, individual collaborators must not publish data concerning participants which is directly relevant to the questions posed in this trial until the first publication of the analysis of feasibility analysis.
All proposed publications will be discussed with and reviewed by the Sponsor prior to publishing other than those presented at scientific forums/meetings. In addition, there is a contractual obligation that the CI should, at the time of submission of any research papers arising from this trial to a peer-reviewed journal, send a copy of the submitted paper to the NIHR Programme issuing the Clinical Doctoral Research Fellowship contract. This is to fulfil reporting requirements. It will also allow a mechanism by which NIHR Programmes can monitor the contractual obligation of researchers to prepare such a research paper on all NIHR funded research.

## 21 Intellectual property

All intellectual property rights and know-how in the protocol and in the results arising directly from the study, but excluding all improvements thereto or clinical procedures developed or used by each participating site, shall belong to KCH/KCL. Each participating site agrees that by giving approval to conduct the study at its respective site, it is also agreeing to effectively assign all such intellectual property rights ("IPR") to KCH/KCL and to disclose all such know-how to KCH/KCL with the understanding that they may use know-how gained during the study in clinical services and teaching to the extent that such use does not result in disclosure of KCH/KCL confidential information or infringement of KCH/KCL IPR.

# 22 Appendices

## 22.1 Appendix 1 - Schedule of assessments

| | Screening (Pre-treatment assessment) | | Intervention phase | | | Follow up assessments | | |
|---|---|---|---|---|---|---|---|---|
| Timepoints | Eligibility < 8 weeks' post diagnosis | Baseline < 8 weeks' post diagnosis | 1st intervention week 1-2 | 2nd intervention | 3rd intervention by week 6 | Mailed Outcome measure booklets and post-trial questionnaire 30 days & 60 days post consent | | 30 days & 60 days post consent |
| Method | Face to face | Face to face | Face to face | Face to face/telephone | Face to face/telephone | Mail | Mail | |
| Informed Consent | | X | | | | | | |
| Demographic data, medical history (disease, treatment, co-morbidities, symptoms) | X | X | | | | | | X |
| Eligibility confirmation | X | X | X | X | X | | | |
| Randomisation | | X | | | | | | |
| AKPS | X | X | X | X | X | | | |
| Assessment (ADL function, priorities, concerns, goals) | | | X | X | X | | | |
| iPoS | | X | | | | X | X | |
| PASE | | X | | | | X | X | |
| SEMCD | | X | | | | X | X | |
| FACT TOI | | X | | | | X | X | |
| EQ-5D-5L | | X | | | | X | X | |
| CSRI | | X | | | | X | X | |
| FACIT-TS-PS & bespoke participant experience questions | | | | | | | X | |
| Adverse Events review | | X | X | X | X | | | x |

Abbreviations: AKPS, (Australia-modified Karnofsky Performance Status) iPOS (integrated palliative outcome scale), PASE (Physical Activity Scale for the Elderly), SEMCD (Self-Efficacy Measure Chronic Disease) FACT TOI (Functional Assessment of Cancer Therapy- Trial Outcome Index), EQ-5D-5L (EuroQol), CSRI (Client Services Receipt Inventory)

## 22.2 Appendix 2 - Protocol Version History

| Version Number | Date | Protocol Update Finalised By (insert name of person): | Reasons for Update |
|---|---|---|---|
| 2 | 27 11 2017 | Joanne Bayly | Addition of sentence to paragraph 1. Page 20, (regarding contacting patients) as a condition from REC committee for favourable opinion. |
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