INSPIRE

Integrated Short-term Palliative Rehabilitation to improve quality of life and equitable care access in incurable cancer: A multi-national randomised controlled trial.

Integrated **S**hort-term **P**alliative Rehabilitation in **I**ncu**r**able Canc**e**r

Trial Identifiers

ISRCTN:	ISRCTN16705336		
REC Number:	To Be Confirmed		
IRAS Number:	328722		
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TRIAL SYNOPSIS

TITLE OF CLINICAL TRIAL:	Integrated Short-term Palliative Rehabilitation to improve quality of life and equitable care access in incurable cancer: A multi-national randomised controlled trial
Protocol Short Title/ Acronym:	**In**tegrated **S**hort-term **P**alliative **Re**habilitation in Incurable Cancer / INSPIRE
Trial Phase if not mentioned in Title:	3
Sponsor Name:	Professor Bashir Al-Hashimi King's College London Room 8.11, 8th Floor Melbourne House, 44-46 Aldwych, London, WC2B 4LL Tel: 02078487306 Email: vpri@kcl.ac.uk
Chief Investigator:	Professor Matthew Maddocks
IRAS:	328722
ISRCTN:	ISRCTN16705336
REC Number:	23/LO/0991
Medical Condition or Disease Under Investigation:	Incurable Solid Cancer
Purpose Of Clinical Trial:	To determine if palliative rehabilitation in addition to usual care is more effective than usual care at improving health-related quality of life in patients with incurable solid cancer
Primary Objective:	To assess the clinical effectiveness of palliative rehabilitation over 8 weeks, on health-related quality of life for patients with incurable cancer.
Secondary Objective(s):	To assess the effectiveness of palliative rehabilitation over 8 weeks on disability, symptom burden and goal attainment for patients with incurable cancer. To assess the cost effectiveness of palliative rehabilitation in terms of the changes in the primary outcome measure of quality of life, and to present cost-utility estimates. To assess cost effectiveness from a health care and societal perspective, focusing on hospital treatment and care costs, ambulatory care costs and cost to informal caregivers, To identify if participant characteristics are associated with clinical effectiveness on quality of life focusing on; sex, gender, age, diagnosis

	(locally advanced or metastatic disease), performance status, and other subgroup factors To determine equity, access, and patient experience of the intervention, across different cultures, socio- economic and other groups, considering gender, age, religious, cultural and personal beliefs. To evaluate whether the palliative rehabilitation intervention was successfully implemented and identify factors contributing to successful integration with existing services.
Trial Design:	Multinational, parallel group, randomised, controlled, assessor blind, superiority trial.
Sample Size:	340 (170 per arm)
Summary of Eligibility Criteria:	Inclusion criteria • Aged 18 years or older. • Diagnosis of incurable solid cancer: lung, colorectal, breast, prostate or other, irrespective of timing in relation to any oncology or palliative care treatments • Eastern Cooperative Oncology Group performance status 2-3 • Able to provide informed consent and complete trial assessments in available languages. Exclusion criteria • Blood cancers: Leukaemia, Lymphoma, Myelodysplastic Syndromes (MDS), Myeloproliferative Disorder (MPD), Multiple Myeloma. • Currently receiving specialist rehabilitation* for their cancer or co-morbidity-related dysfunction, or received within the two weeks prior to consent. • Clinician rated prognosis of less than 3 months. **See definition in glossary*
Outcomes:	**Primary outcome** • Health related quality of life - Functional Assessment of Cancer Therapy (FACT) General scale at 8 weeks **Secondary outcomes** • Functional Assessment of Cancer Therapy (FACT) General scale at 4 and 16 weeks • Disability - World Health Organization Disability Assessment Schedule (WHODAS 2.0) at 8 and 16 weeks • Symptoms- Partial Integrative Palliative care Outcomes Scale (IPOS) at 8 and 16 weeks • Goal attainment- Goal attainment scale (GAS-Light) at 8 and 16 weeks • Client Service Receipt Inventory at 8 and 16 weeks **Implementation outcomes:** • Acceptability - Acceptability of Intervention Measure (AIM) and bespoke questionnaire • Appropriateness - Intervention Appropriateness Measure (IAM) and bespoke questionnaire • Access – semi-structured qualitative interviews
Maximum Duration of Participation in the Trial:	16 weeks (28 weeks for survival data)

Overall trial duration	24 month
Intervention (Description, frequency, details of delivery)	The intervention being tested is Integrated Short-term Palliative Rehabilitation. It comprises up to 3 manualised sessions (face to face and/or remotely (via telephone or video call) delivered by a rehabilitation practitioner (typically a physiotherapist or occupational therapist). Core components focus on (i) self-management of symptoms, (ii) physical activities and fitness, and (iii) social participation, with explicit use of behaviour change techniques with goal setting and action planning. The rehabilitation practitioner works in partnership with the person with incurable cancer, and those important to them, to support and optimise their function. Sessions focus on outcomes each person has said are important to them. The rehabilitation practitioner attends to practical, physical, emotional, psychological, and existential concerns impacting on function, either directly within the intervention or indirectly through onward referral. The intervention allows for individual tailoring and flexibility in location, timing and frequency of sessions and content over a 7-week intervention period. Participants can receive a minimum of two rehabilitation sessions and a maximum of three rehabilitation sessions. It is delivered in addition to any usual services delivered by the participant's oncology team and palliative care team.
Comparator Intervention:	Unrestricted usual care, as determined by the healthcare system in the participating countries, within oncology, palliative care, other hospital services or health services in the community and medical practitioner(s) in charge of their care. This will include usual referral to any existing rehabilitation services.
Version and Date of Final Protocol:	V1.0, 17 November 2023
Version and Date of Protocol Amendments:	N/A

REVISION HISTORY

Protocol version	Description of changes from previous revision	Effective Date

GLOSSARY OF TERMS

95% CI	95% Confidence Interval
ADL	Activities of Daily Living
AE	Adverse Event
AM-PAC-CAT	Activity Measure for Post-Acute Care, Computer Adaptive Test version
ANCOVA	Analysis of Covariance
AUSL	Azienda Unità Sanitaria Locale
BMC	BioMed Central
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CI	Chief Investigator
COM-B	Capability, Opportunity, Motivation-Model
COMET	Core Outcome Measures in Effectiveness Trials
(e)CRF	(electronic)Case Report Form
CSI	Cicely Saunders Institute
CSRI	Client Service Receipt Inventory
DCR	Data Clarification Request
DMC	Data Monitoring Committee
EAPC	European Association for Palliative Care
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ECPC	European Cancer Patient Coalition
EDC	Electronic Data Capture
FACT-G	Functional Assessment of Cancer Therapy - General
FAIR	Findability, Accessibility, Interoperability, and Reusability
FCI	Functional Comorbidity Index
GAS - Light	Goal Attainment Scaling - Light
GCP	Good Clinical Practice
HCL	Hospices Civils de Lyon
HRQoL	Helath Related Quality of Life
ICH	International Council for Harmonisation
IRCCS	Istituto di Ricovero e Cura a Carattere Scientifico
ISRCTN	International Standard Randomised Controlled Trial Number
JRC	Joint Research Centre
KCTU	King's Clinical Trial Unit
INT	Istituto Nazionale dei Tumori di Milano
KORDS	King's Open Research Data System
LME	Linear Mixed Effects (analysis method)
MAR	Missing at Random
MD	Doctor of Medicine
NHS	National Health Service
NO	Norway
NSCLC	Non-Small Cell Lung Cancer
IPOS	Integrated Palliative care Outcome Scale
PPI	Patient and Public Involvement
PROMs	Patient Reported Outcome Measures
QALY	Quality-Adjusted Life-Year
QoL	Quality of Life
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
UEDIN	The University of Edinburgh
UiB	Universitetet i Bergen
UK	United Kingdom
US	United States
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Schedule
Specialist Rehabilitation	A rehabilitation intervention that is delivered by a single professional or a multi-disciplinary team (physiotherapist, occupational therapist, dietician, speech and language therapist, physiatrist, rehabilitation nurse) that includes a holistic functional needs assessment, goal setting and goal action planning, and intervention elements to address symptoms, physical activity, mobility, , and social participation.

PROTOCOL CONTENTS

1. INTRODUCTION

1.1 BACKGROUND & RATIONALE

Cancer is one of the main causes of illness, burden and death in Europe. The Joint Research Centre (JRC) of the EU estimated 2.7 million new cancer cases and 1.3 million deaths in 2020 in people over 65 years of age [1]. For all cancers, between 53-79% of men and 41-62% of women are diagnosed with incurable disease [2]. Their cancer treatment is life-prolonging but will not cure the disease. Survival rates are increasing overall, but least so for older people [3]and those with multimorbidity which are both are growing populations. The total cost of cancer in Europe reached €199 billion in 2018, with equally large costs within and outside the health-care system [4].

Cancer is also a major and growing contributor to disability (loss of function). Recent global estimates suggest a loss of 382 disability-adjusted life years per 1000 individuals [4]. People with cancer rank loss of function among the most common unmet supportive care needs [5-8]. Disability is a poorly recognised and undertreated consequence of incurable cancer [9]. It can occur because of the disease, its treatment, and related symptoms (e.g., breathlessness, pain, fatigue) [10] and syndromes (e.g., cachexia, sarcopenia) [11]. Over time, loss of function results in people not being able to continue with valued roles and routines, to manage usual household and social activities, and to self-care. One-third of adults with cancer require assistance to perform basic activities like washing and dressing, and half need help with extended activities like shopping and transportation [9]. Disability reduces quality of life and well-being [5-8] and increases burden on informal carers including family members[12] and/or formal care services including demand for hospital or nursing care. Disability related to daily activity is closely related to unplanned hospital admissions and mortality [11].

Palliative rehabilitation empowers people with incurable conditions to actively manage their condition themselves, enabling them to live fully and enjoy the best health-related quality of life possible [13, 14], including cancer towards the end of life [15]. It aims to reduce symptoms and help people to stay independent and socially active. WHO policy on Universal Health Coverage states both rehabilitation and palliative care as essential, quality health services. [16, 17]. It recommends they be integrated within and between primary, secondary and tertiary health systems using a multi-professional workforce. While integrated rehabilitation has been achieved for people with chronic respiratory [18], cardiac [19] and stroke conditions [20, 21], this is not the case for people with cancer, especially those living with incurable disease. Access to palliative care services has increased but access to rehabilitation remains varied.

State of the art palliative rehabilitation trials include:

- a collaborative tele-rehabilitation programme for people with solid or haematological cancers, supplemented with telephone support from nurses for pain management, which achieved improvements in the primary outcome basic mobility, pain and quality of life [26].
- a trial testing tailored, supervised home-based rehabilitation with nurse led symptom support delivered by telephone, which did not achieve improvements in the primary outcome, 6-minute walking distance, but found improvements in a secondary outcome, symptoms, at 6 months[27].
- a multi-professional rehabilitation programme, including exercise, within a palliative care clinic for people with newly diagnosed solid tumours, which found improvements in the primary outcome quality of life [28].

These trials show the high relevance of interdisciplinary team working [26, 28] and perspective [29], the need to ensure a relevant population with evidence of need [26, 27, 29], and the requirement to balance component interventions with attention to symptom self-management, physical and social function [28]. The single country nature of studies limits generalisability, and there is limited study around cost effectiveness and economics (confined to the US setting), which prevent uptake from payers and policy makers. Practice changing evidence is still required.

Integrated Short-term Palliative Rehabilitation in incurable cancer was developed to meet specific functional needs and goals of people living with incurable cancer following UK Medical Research Council

guidance for complex interventions. [22]. Development work included a systematic review [23], exploring the application of behaviour change approaches in empirical rehabilitation studies, and focus groups with patients, family members and clinicians, [24] In brief, it combines previously tested symptom self-management, physical activity and exercise, and goal orientated approaches [24, 25] across up to 3 sessions (face to face and/or by telephone) delivered by a rehabilitation practitioner (physiotherapist, occupational therapist, or rehabilitation nurse) [25]. Our parallel group randomised controlled multi-site feasibility trial tested Integrated Short-term Palliative Rehabilitation in people with thoracic cancer. It achieved the primary feasibility endpoints; 54 of 159 (34%) eligible patients and 44/54 (82%) and 39/54 (72%) participants provided data at 30 days and 60 days respectively. Secondary outcomes also demonstrated clear feasibility for effectiveness testing. Intervention fidelity was high: 25/26 participants allocated to integrated rehabilitation received a median 3 (range 1-3) sessions of rehabilitation over 32 (22-45) days. Trial and intervention satisfaction were high. Changes in clinical outcomes were most apparent for health-related quality of life as measured by FACT-L score, median (interquartile range) change 9.7 (−12.0 to 16.0) rehabilitation versus 2.3 (−15.0 to 14.5) usual care. We now need to test effectiveness at scale, across multiple health systems, to achieve our ambition to transform care accessed by people with incurable cancer in Europe.

2. Trial Objectives

2.1 Primary Objective:

To assess the clinical effectiveness of palliative rehabilitation over 8 weeks on quality of life, measured using FACT-G, as compared to usual care.

2.2 Secondary Objectives:

To assess the effectiveness of palliative rehabilitation over 8 weeks on disability, symptom burden and goal attainment for patients with incurable cancer.

To assess the cost effectiveness of palliative rehabilitation in terms of the changes in the primary outcome measure of quality of life, FACT-G, and to present cost-utility estimates.

To assess cost effectiveness from a health care and societal perspective, focusing on hospital treatment and care costs, ambulatory care costs and cost to informal caregivers over 8 weeks.

To identify which participant characteristics are associated with beneficial randomised intervention effect on quality of life focusing on; sex, gender, age, diagnosis (locally advanced or metastatic disease), performance status, and other subgroup factors.

To determine equity, access and patient experience of the intervention, across different cultures, socio-economic and other groups, considering gender, age, religious, cultural and personal beliefs.

To evaluate whether the palliative rehabilitation intervention was successfully implemented and identify factors contributing to successful integration with existing services.

3. Trial Design

This is a multinational, multicentre, phase 3, randomised, controlled trial to determine if palliative rehabilitation and usual care is more effective than usual care alone in patients with incurable solid cancer. Participants will be randomised in a 1:1 ratio. Participants will be followed up at weeks 4, 8 and 16. Participants will be in the trial for up to 28 weeks from randomisation until the medical notes review to collect survival data at week 28 or at their death, whichever comes first.

If not terminated earlier, the expected duration of the trial is 24 months from opening to recruitment of the first participant to final assessments of all trial participants, cleaning and locking of the trial database.

4. PARTICIPANTS

4.1 STUDY SETTINGS & RECRUITMENT

Through our pre-assessment of organisational alignment across oncology, palliative care and rehabilitation services, we will target recruitment from oncology services where rehabilitation provision in usual care is low. Recruitment will occur in oncology or palliative care outpatient and, where possible, community services in the participating countries.

LIST OF STUDY COUNTRIES:

United Kingdom
Denmark
Norway
France
Italy

4.2 ELIGIBILITY CRITERIA

4.2.1 INCLUSION CRITERIA

- Age 18 years old or older
- Diagnosis of incurable solid cancer: lung, colorectal, breast, prostate or other, irrespective of timing in relation to any oncology treatments and/or palliative care
- Eastern Cooperative Oncology Group (ECOG) performance status 2-3
- Able to provide informed consent and complete trial assessments in available languages

4.2.2 EXCLUSION CRITERIA

- Blood cancers: leukaemia, lymphoma, Myelodysplastic Syndromes (MDS), Myeloproliferative Disorder (MPD), multiple myeloma
- Currently receiving specialist rehabilitation* for their cancer or co-morbidity-related dysfunction or received within two weeks prior to consent
- Clinician rated prognosis of less than 3 months

*See glossary for definition of specialist rehabilitation

4.3 INFORMED CONSENT

No trial procedures will commence before the participant gives their fully informed consent and signs the trial consent form.

Informed consent will be obtained by the Principal Investigator or delegated researcher at each site, following personal explanation of the trial procedures.

If a participant is physically unable to sign the consent form, verbal consent in the presence of an impartial witness can be documented on the consent form and the participant signature should be marked with an X. The impartial witness can be participants carer or relative, however cannot be affiliated with the trial, hospital or the research team. The following text should be written on the form: 'Participant physically unable to sign consent but has given verbal consent in the presence of *[name, relationship to clinic or participant, contact information]*'. The witness should sign the witness line on the consent form and the investigator/researcher should sign the consent form as normal. Participants who lack capacity to provide verbal consent are not eligible to participate.

The original signed consent form will be retained by the research team. A copy will be given to the participant and a copy will be added to the participant's medical record. Individuals who decline to take part in the trial, may be asked if they would like to provide a reason of their decision to decline, to inform a qualitative analysis around equity and inclusivity. When asked for the reason for their decision, individuals will be informed about this purpose and re-assured that they do not have to provide any reason about their decision. They will be informed that their rights and access to usual care will not be affected.

If individuals who decline taking part in the trial provide the reason for their decision, the reason will be registered anonymously and no other data will be collected. In this case, a verbal agreement to use data will be sought instead of consent.

4.4 WITHDRAWAL

Trial participants have the right to withdraw their consent to participate at any time and for any reason. Their decision to withdraw will not affect the routine care they receive or result in loss of benefits to which they would otherwise be entitled. Participants who withdraw consent will discontinue their future participation in the trial. With consent trial research data obtained to the point of withdrawal will be included in the analysis. In some countries it is a regulatory requirement that participants are given the opportunity at the point of withdrawal post randomisation to request that all data collected during the trial to be withdrawn. As the KCTU Randomisation system does not allow data removal once it has been registered in the system, a code (e.g. “XX”, “XXX”) will be used instead of participants initials in countries where data withdrawal is a regulatory requirement.

Participants are not required to give any reason for withdrawal; however, the research team may ask for this information in countries where this is permitted to inform an equity and inclusivity analysis.

Please refer to section 8. Withdrawal of Participants for more information on different levels of withdrawals.

5. TRIAL INTERVENTIONS

5.1 THERAPY/INTERVENTION DETAILS

The intervention being trialled is Integrated Short-term Palliative Rehabilitation.

It is underpinned by a strong theoretical framework relevant to problems experienced by people with incurable cancer that are amenable to change through rehabilitation. These include theories of disease and illness (to identify modifiable factors in the individual person in their unique context); WHO International Classification of Diseases [30]; WHO International Classification of Functioning, Disability and Health [31, 32]; Common Sense Model of Self-Regulation [33]; and phenomenology of illness [34-36]; and theories of change (to predict and explain how the intervention components influence the modifiable factors); Wade’s Rehabilitation Process [32, 37]; and behaviour change theory (Capability, Opportunity, Motivation-Model (COM-B) [38].

These support a tailored, person-centred approach that allows each person to give a narrative account of their own experience and immediate concerns. Bringing this narrative together with a rehabilitation practitioner, situated within the wider local multi-professional team, form the underlying conceptual model (Figure 1).

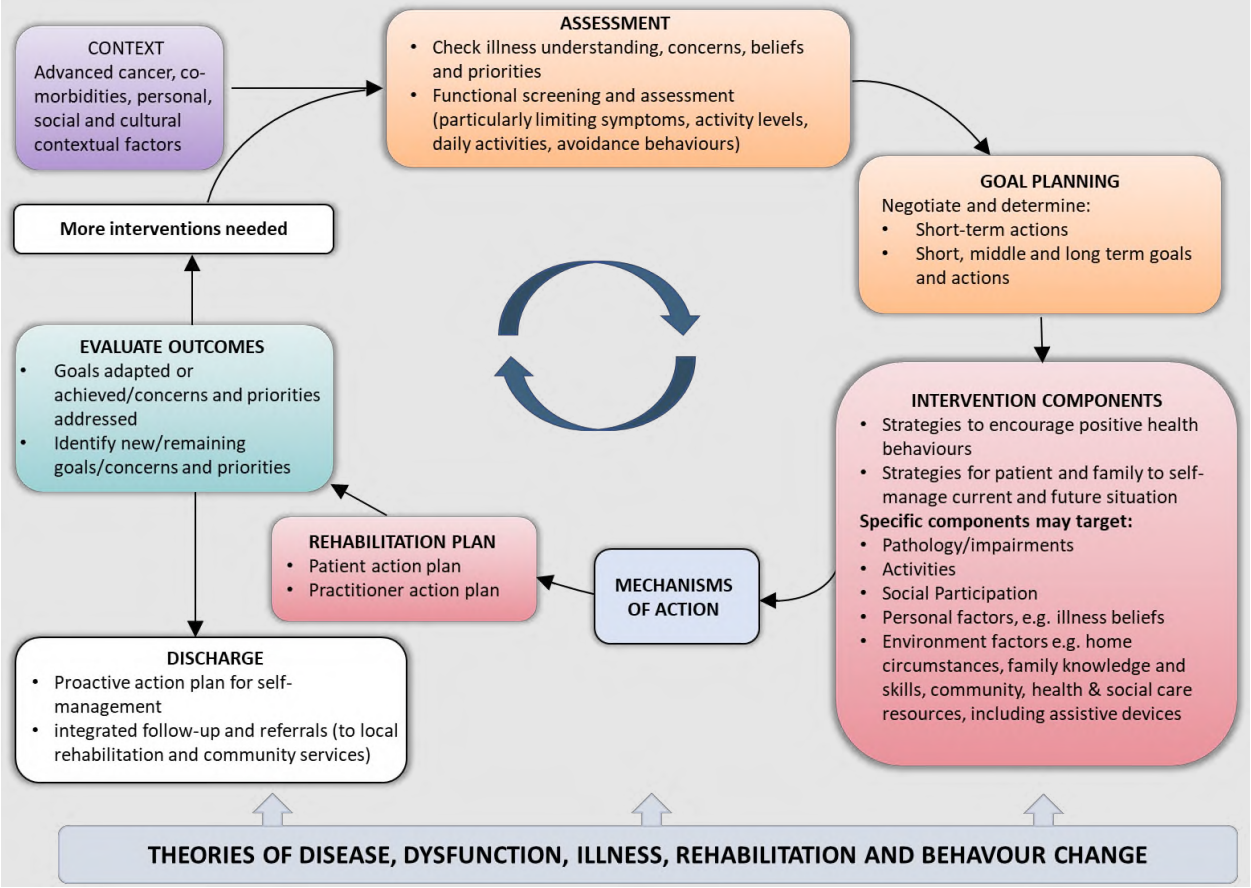

FIGURE 1 UNDERLYING CONCEPTUAL MODEL OF THE INTERVENTION.

Participants will be offered up to 3 manualised sessions (face to face and/or remotely, via telephone or video-conference) delivered by an expert rehabilitation practitioner (physiotherapist, occupational therapist,).

Core components focus on (i) self-management of symptoms, (ii) physical activities and fitness, and (iii) social participation. Delivery of rehabilitation intervention components will include explicit use of behaviour change techniques including goal setting and action planning to focus on outcomes that are meaningful for the person, their family, and clinicians [56].

5.1.1 MAIN MODIFIABLE FACTORS/INTERVENTION TARGETS:

Modifiable factors/intervention targets that can be changed through interaction with rehabilitation intervention include [39, 40]:

- Physical activity and fitness [38, 48-52]
- Participation in usual daily activities and social participation [53-56]
- Symptom self-management (including fatigue, cough, breathlessness, pain, sleep, dietary intake and appetite) [43, 44, 57-59]
- Function supporting and limiting knowledge, perceptions and beliefs held by patients, family/friends, clinicians [53, 59-63]
- Use of assistive devices and mobility aids [56, 63]
- Structural factors limiting function (stairs, home location, access to resources)
- Muscle function and/or cachexia [64]
- Psychological well-being, including hope, confidence, and control [24].

The rehabilitation practitioner will work in partnership with the person with incurable cancer, and those important to them, to support and optimise their independence and interdependence.

The rehabilitation intervention will focus on outcomes each person has said are important to them and the intervention allows for individual tailoring and flexibility in timing and content.

The first session will cover the aims and scope of the intervention, followed by a person-centred assessment using principles of motivational interviewing to engage and elicit concerns. The rehabilitation practitioner and participant will agree priorities and concerns to be addressed. Carers and family members will be involved where present. Intervention components will be selected and personalised as needed, then set out in an individualised rehabilitation action plan. Access to suppliers of assistive equipment and a directory of local health, social and community services to support onward referral will be established during trial set up at each site.

The second and third sessions both review the participant's status, priorities, concerns, and action plan items from previous session(s). A rehabilitation action plan, including signposting to other relevant health and community services, will be introduced, and finalised at the end of these sessions.

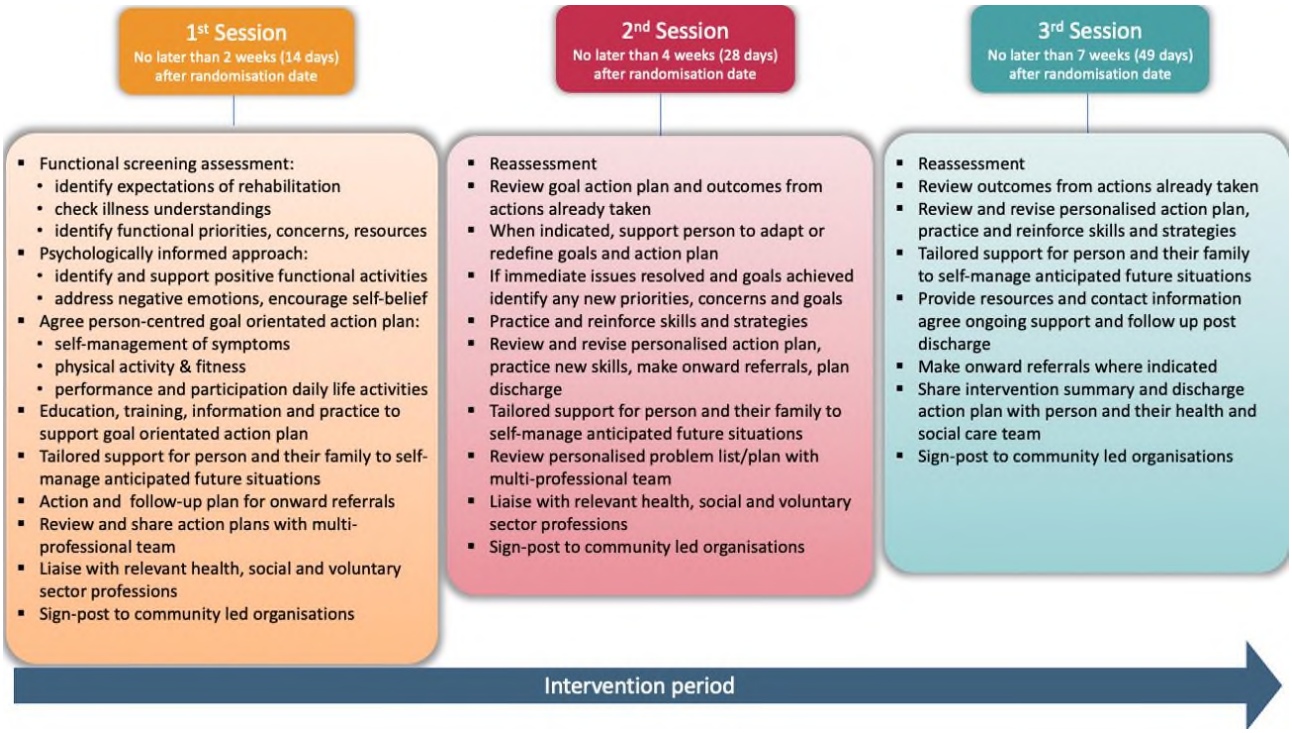

FIGURE 2 TIMELINE AND FOCUS OF THE INTERVENTION SESSIONS

5.2 FREQUENCY, DURATION AND LOCATION OF REHABILITATION INTERVENTION SESSIONS

Participants will receive up to three rehabilitation sessions with a rehabilitation practitioner. Rehabilitation practitioners will contact participants (according to locally accepted procedures and regulations) by text, telephone or email to arrange appointment times and location details. It is expected that the intervention sessions will each last 30-90 minutes, depending on individual participant circumstances.

5.2.1 FIRST SESSION:

All participants will receive a rehabilitation session conducted face to face. This should occur as close to randomisation as can be arranged, but no later than 14 days after date of randomisation. The first session will be conducted face to face, in a health care setting or in the participant's home.

5.2.2 FOLLOW ON SESSIONS:

The second rehabilitation session can be conducted remotely (by telephone or videoconference) or face to face, in a health care setting or in the participant's home. It should take place as soon after the first session as is agreed by the participant and the rehabilitation practitioner, but no later than 4 weeks (28 days) after date of randomisation.

The third and final rehabilitation session will be conducted remotely (by telephone or videoconference) or face to face, in a health care setting or in the participant's home. It should take place as soon after the second session as is agreed by the participant and the rehabilitation practitioner, but no later than 7 weeks (49 days) following date of randomisation.

5.2.3 Rehabilitation Intervention Completion

It is anticipated that most participants will complete and be discharged from the intervention after receiving three rehabilitation sessions. The rehabilitation intervention is considered sufficiently complete when a participant has a rehabilitation action plan.

Where a participant reports that the rehabilitation intervention has met all their needs, and they do not want a third session, they can be provided with a rehabilitation action plan during the second rehabilitation intervention session. In this instance, they will be offered a follow-up telephone or video-conference call. If they accept, then this call will be documented in the Rehabilitation Data Collection Booklet (for practitioners) as a third rehabilitation session. If they decline, it is documented that they completed the intervention after the second rehabilitation session.

5.3 Data collection Booklet (for practitioners)

Data collection during intervention delivery to comply with reporting guidelines[41] includes:

- the location, mode of delivery, number, timing and duration of intervention sessions
- procedures followed, including:
  - strategies for symptom self-management; physical activity and fitness; social participation
  - behaviour change techniques and goal action planning
  - rehabilitation plan agreed and shared with participant and wider team
  - signposting and/or referral to other health and/or community services
- materials used during intervention delivery or provided to participants, (including equipment, leaflets, web links etc.)

Rehabilitation practitioners will document any deviation from the protocol in the rehabilitation data collection booklet. This will include if planned rehabilitation sessions were missed or outside the planned visit windows.

5.4 Adherence to the trial intervention

Methods to improve adherence to the intervention and to overall trial retention include:

a) Standardised initial and ongoing training of the rehabilitation practitioners with:
   - a culturally congruent intervention manual
   - pre-trial culturally congruent asynchronous and synchronous training
   - Familiar supporting resource materials for use by trial rehabilitation practitioners during intervention delivery in local resource packs, harmonised across sites.

b) Training of intervention practitioners will include building rapport and goal setting with participants living with incurable cancer and use of essential and desirable behaviour change techniques (BCTs) as described in the intervention manual.

c) Tailoring of intervention components to address participants goals.
d) Accessible participant held rehabilitation action plan.
e) Including a family member or friend involved in providing informal care in the delivery of the intervention, to optimise understanding and support for participant.

5.5 USUAL CARE

Participants recruited to the trial allocated to either the intervention arm or the usual care arm will continue to be eligible for, and to receive all services routinely provided by their health care team following usual assessment and referral procedures. The control arm will receive usual care alone.

6. DATA COLLECTION AND DATA ENTRY

6.1 INITIAL SCREENING AND ELIGIBILITY ASSESSMENT

Potentially eligible participants will be introduced to the research trial by the health care professionals in oncology or palliative care outpatient clinics and via community/home oncology and palliative care services. Members of the potential participant's direct care team (oncology, palliative care or community) will assess eligibility during routine assessments and may also screen the list of people attending clinics or on their caseload to identify those who meet the eligibility criteria. The health professionals will provide potential participants with the brief trial flyer and ask for permission to pass their contact details to the research team.

The research team will provide the potential participant with the full trial information leaflet and discuss the trial with them in detail. This will include full details of what is involved for them if they agree to participate in terms of the intervention and data collection and their right to withdraw at any point, either in person, or by phone, video call or email, (as per the patient's preference). In all cases, participants will be given at least 24 hours to consider their participation in the trial before completing consent processes. This delay will be waived if the patient wishes to participate and states that it is more convenient for them to complete the consent form and baseline questionnaire the same day. No trial procedures will commence before the participant gives their fully informed consent and signs the consent form.

A copy of the consent form will be given to the participant and the original retained by the research team with a copy placed in the participant's medical record.

6.2 PARTICIPANT TIMELINE

Timepoint		Baseline (≤10 days after screening)	Week≤ 2 (1st rehabilitation intervention)	Week 4 Data collection	Week ≤4 post randomisation (2nd rehabilitation intervention)	Week ≤7 post randomisation (3rd rehabilitation intervention)+	Week 8 Data collection	Week 16 Data collection	Ongoing
Assessment and intervention contact		Face-to-face	Face-to-face	Independent or with investigator	face-to- face or remote	face-to- face or remote	Independent or with investigator	Independent or with investigator	
Form:									
1	Informed Consent	x							
2	Registration Form	x							
3	Socio-demographic data	x							
4	Eligibility review	x							
5	Medical History (Comorbidities, clinical diagnosis, treatment history, blood tests results, nutrition and physical activity history)	x							
6	Randomisation	x							
7	AIM, IAM, bespoke questionnaire *		x**				x**		
8	Rehabilitation Data Collection Booklet (for practitioners) *		x**		x**	x**			
9	Status form			x			x	x	
10	FACT-G (Primary Outcome)	x		x			x	x	
11	WHODAS 2	x					x	x	
12	IPOS (Physical Symptoms)	x					x	x	
13	Adapted GAS-Light	x					x	x	
14	Modified Client Service Receipt Inventory (CSRI)	x					x	x	
15	Hospital Admissions log								x
16	Adverse Events Log								x
17	Withdrawal form								x

*Participants randomised to the intervention arm only (secondary database)
** Questionnaires/booklets differ for each timepoint
*** Offered to participants who opted-out from 3rd Rehabilitation Intervention visit
+ Session is optional. If participant opts-out then a follow up phone/video call will be offered and documented in the Rehabilitation Data Collection Booklet

TABLE 1. SCHEDULE OF EVENTS

6.2.1 TRIAL FLOWCHART

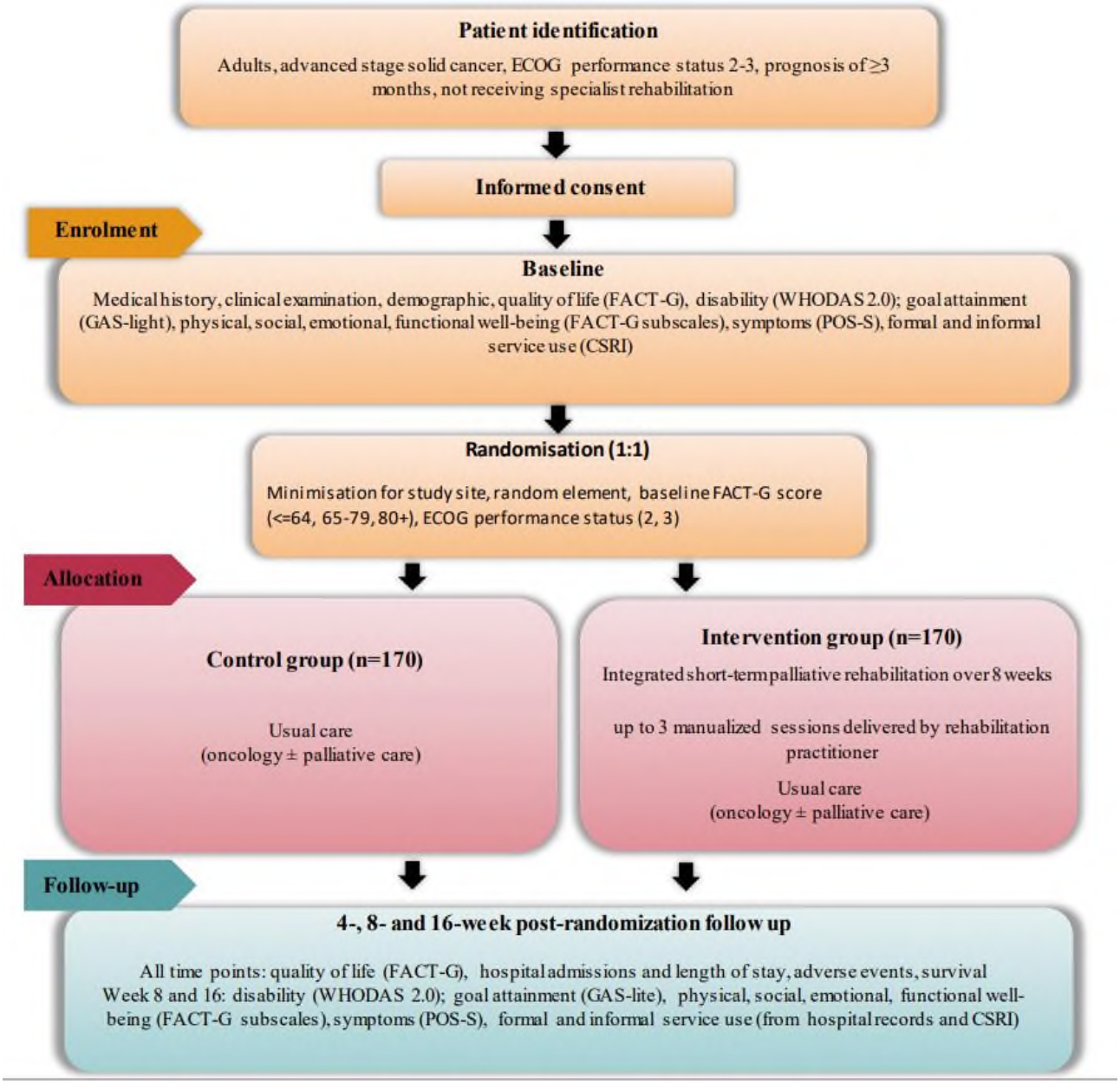

FIGURE 3 TRIAL FLOWCHART

6.3 VISIT WINDOWS

The baseline visit can be scheduled up to 10 days after the participant has been approached for initial screening by the site study team. Follow-up visits are scheduled at weeks 4, 8 and 16 post randomisation for PROM and fidelity data capture.

For participants randomised to receive the rehabilitation intervention, visits are scheduled no later than 2 weeks post-randomisation and then at no later than week 4 and no later than week 7 post randomisation.

If a visit is later than the target visit, this visit should be scheduled as soon as possible, and the data should be entered at the intended visit. The subsequent visit should be scheduled as per original schedule. A timepoint is considered missed if the visit is not conducted by the start of the subsequent visit window.

6.3.1 Baseline visit

Baseline assessments will be conducted only after a participant signs an approved Informed Consent Form. Baseline data will be collected as per the Schedule of Events in Table 2 above for the baseline visit and ongoing sections. Eligibility criteria will be confirmed at the baseline visit. During this visit, participants will be randomised.

6.3.2 Rehabilitation intervention visits

Participants randomised to the intervention will participate in up to three rehabilitation visits. (See section 5.2). Rehabilitation intervention should be completed before, and no later than the end of week 7 (49 days) after randomisation.

6.3.3 Weeks 4, 8 and 16 data collection (PROMs and Fidelity) visits

Follow up data (PROMs) will be collected as per Schedule of Events in Table 2 for the relevant visits and ongoing section. The visits can be scheduled within a window of +/- 5 days from the original date. Each visit will be completed by participants independently or with the study researcher. It should be indicated in the data collection form if the visit was completed independently, with the caregiver, or with the researcher.

A status form and questionnaire completion form will be completed at these time points; in the event of a missed timepoint, a both forms must be competed.

In cases where the participant completes the study, a withdrawal form should be completed during medical notes review at week 28 only to indicate the participant did not withdraw.

6.4 Data Entry

6.4.1 Randomisation

Randomisation will be undertaken by authorised site staff on the randomisation system by going to www.ctu.co.uk and clicking the link to access the randomisation system. A full audit trail of data entry will be automatically date and time stamped, alongside information about the user making the entry within the system.

Please refer to the Randomisation User Guide provided separately for more details.

6.4.2 Macro eCRF

There are two databases in the trial: main and secondary. The secondary database has been designed to capture data related to the rehabilitation intervention and to prevent unblinding of the blinded trial team members. Source data will be entered by recruiting site staff, typically within 7 days of data collection by authorised staff onto the EDC by going to www.ctu.co.uk and clicking the link to access the MACRO 4 EDC system. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

Study site staff will be delegated by the site PI to access the eCRF and randomisation systems via a Study Site Delegation Log. The request for user access must go to the UK Trial Manager, who will submit user requests for all sites to the KCTU team upon receipt of completed Study Site Delegation Logs. Requests for user access will be processed within a maximum of 5 working days.

Training videos for data entry staff, study site monitors and trial managers / trial co-ordinators are available at www.ctu.co.uk/training-events/ under the 'Access Training' section.

For more details see section 13. Data Management.

6.5 PRE-RANDOMISATION DATA COLLECTION

6.5.1 REGISTRATION

When the participant has signed consent, the study site staff should register the participant in the MACRO eCRF system. Upon registration, the system will assign a unique study PIN (Participant Identification Number), to be used for the participant throughout the study for the randomisation system and the secondary eCRF. The study PIN will ensure that the participant's data remains anonymous to the central research team.

6.5.2 ELIGIBILITY

All eligibility checks must be completed, and the researcher must confirm eligibility prior to randomisation.

6.5.3 SOCIO-DEMOGRAPHICS

Relevant demographic information, such as participants initials (in countries where this is permitted), gender, age, relationship status, living situation, having children, educational level, employment status, financial situation, geographical access to secondary health care, religious status, social support from family or friends, ongoing stressors, perceived discrimination by health care system and others, and health confidence (a broad concept encompassing aspects of self-efficacy, patient activation, health literacy, self-management, shared decision-making, capability, and empowerment, ethnicity (in countries where collection of ethnicity data is permitted), and contact details (telephone number, email address, postal address) will be collected prior to randomisation.

6.5.4 MEDICAL HISTORY, (CLINICAL DIAGNOSIS, TREATMENT AND COMORBIDITIES)

Relevant medical history and comorbidities will be recorded. The clinical diagnosis, date of diagnosis, current treatment, comorbidities (predefined in Charlson Comorbidity Index (CCI)[42], items from Functional Co-morbidity Index [ref], Body Mass Index (BMI), weight change (to record significant weight loss), nutrition and physical activity history, blood test results will be recorded during screening.

6.5.5 RANDOMISATION (MINIMISATION)

Randomisation should take place as soon as possible after consent is obtained and eligibility confirmed. Randomisation will be by the method of minimisation. It is vital that baseline assessments are performed prior to randomisation as the FACT-G and ECOG baseline scores are used as minimisation factors and to ensure that randomisation does not influence baseline assessments. Site must confirm in the eCRF system whether participants were randomised into the study or not.

The randomisation procedure and access to the randomisation system is described in the Randomisation User Guide provided separately.

6.6 ASSESSMENT OF EFFECTIVENESS

The effectiveness of the rehabilitation intervention will be determined by validated participant-reported outcome measures (PROMs). The PROMs are collected via the questionnaire booklet completed in person with a member of the research team or independently, and (e)mailed (accordingly with the local procedures and guidelines) to delegated members of the research team at each site. The PROMs should be recorded on the eCRF.

6.6.1 Primary outcome measure: FACT-G

The primary outcome is health-related quality of life over the last 7 days as assessed by the Functional Assessment of Cancer Therapy (FACT) General scale total score (0=worst quality of life to 108=best quality of life) at 8 weeks after randomisation [43]. FACT-G comprises 28 items across four domain subscales: physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items) and functional well-being (7 items). Item scores range from 0-4: not at all (0), a little bit (1), somewhat (2), quite a bit (3), very much (4). Scoring guidelines are used to convert item scores in domain sub scores. Domain sub scores are summed into a FACT-G total score.

FACT-G is most able to capture the impact of the Short-term Integrated Rehabilitation Intervention. Previous studies of palliative rehabilitation interventions have identified that patient reported measures evaluating discrete outcomes, such as physical activity or confidence, were not relevant to all participants [24, 44]. FACT-G captures change in domains directly influenced by our intervention [45, 46] when considering our inclusive approach to eligibility, the varying needs within the population, and the bi-directionality of functional trajectories. This takes into account findings from a trial of home-based rehabilitation for inoperable lung cancer, which found significant improvements in health-related quality of life and symptom burden, without change in physical function as measured by the 6-minute walking test [27].

6.6.2 Secondary outcome measures:

The secondary efficacy parameters are based on responsiveness to rehabilitation interventions and core outcome sets in cancer recommended by the COMET Initiative and will be assessed.

The secondary outcomes (WHODAS 2.0 [69], adapted Goal Attainment Scale-Light measure [70], FACT-G subscales [65] and IPOS (Physical symptoms) [71] will support evaluation of the level of tailoring delivered and whether we achieved our intention to deliver person-centred rehabilitation. The evaluation of secondary endpoints will contribute data for analysis of mechanisms and mediators of action of the intervention on any changes observed in health-related quality of life observed. Client Services Receipt Inventory (CSRI) [47] will inform health economic evaluation.

FACT-G Subscales

Scores for each of the FACT-G domain subscales will be assessed as the physical wellbeing, social wellbeing, emotional and functional wellbeing sub-scores.

WHODAS 2.0

WHODAS 2.0 comprises a 36-item questionnaire with 6 domains: understanding and communicating=6 items; getting around = 5 items; getting along with others = 5 items; self-care – 4 items; life activities=8 items (4 items related to work/school are optional); societal participation=8. Each item is scored on a scale of 1-5 based on activity difficulty (1=none, 5=extreme/cannot do). These sub scores are combined into a WHODAS 2.0 summary score, which ranges from 36 (no difficulty) to 180 (extreme difficulty).

WHODAS 2.0 [48] is a measure of global disability and participation based on the domains of the World Health Organisation International Classification of Functioning, Disability and Health, which underpins the palliative rehabilitation intervention. A recent study found this measure could discriminate levels of difficulty during daily activities experienced by people reporting independent function in other measures of basic and instrument activities of daily living [49].

Adapted Gas-Light

The adapted Goal Attainment Scale [50] will evaluate the extent to which people achieve or partially achieve important goals established during the intervention. It measures achievement of a person's goals rather than a change in health status and accounts for baseline function and the degree of goal difficulty. Goals are rated in relation to their importance to a person and difficulty on a scale of 0-3. A 6-point rating scale is then used to record the extent to which a personal goal was achieved (-2=no change or got worse; 0=as expected; 2=much better than expected). This information is transformed numerically to produce a GAS t-score for each participant ranging from 0-100 that accounts for the characteristics and level of attainment for each goal (0=low difficulty/importance, goals not achieved; 100=high difficulty/importance, goals achieved to a much better degree than expected).

IPOS (Physical Symptoms)

Integrative Palliative care Outcome Scale- (IPOS) (Physical Symptoms) comprises a 10-item questionnaire with the option to add additional symptoms, rated from 0=not affected to 4=overwhelmingly affected. The scores for each symptom are combined to produce a summary score ranging from 0 (not affected) to 80 (overwhelmingly affected). IPOS is a brief patient-reported measure that captures change in a range of concerns prioritised by people with advanced illness, including self-reported main concerns, common symptoms, patient/family distress, existential distress, sharing feelings with family or friends, information received and practical concerns [51].

Modified CSRI

Modified Client Services Receipt Inventory (CSRI) [47]: assesses hospital admissions, emergency attendances and other health service use including inpatient, outpatient, community-based, and home-based services. Each item is assessed individually using a Yes/No response and recorded as prevalence.

Rehabilitation Data Collection Booklet (for practitioners)

To assess fidelity to the rehabilitation intervention, including how well participants enacted the elements within their rehabilitation action plan, at the beginning of the second and third intervention visit, the rehabilitation practitioner will ask the participant for details on how they have followed and/or modified their rehabilitation action plan. This information will be recorded in the Rehabilitation Data Collection Booklet.

6.6.3 Safety, survival, and health economic outcomes

Safety and survival will be assessed on an ongoing basis. Health economic outcomes will be assessed at weeks 8 and 16. Safety will be report based on the occurrence of SAEs, and occurrence of deaths; adverse (please see section 16. Adverse Events Management and Reporting).

Hospital Admissions

Hospital admissions will be collected from the medical records. All hospital admissions will be recorded on an ongoing Hospital Admissions Log by delegated members of the research team at each site stating the length of the admission (start and end date)

ADVERSE EVENTS LOG

During each visit, participants will be asked about adverse events (see section 14). All adverse events will be recorded in an ongoing Adverse Events Log stating start/end date, severity, serious adverse event, relatedness to the rehabilitation intervention, impact on the ability to receive rehabilitation and outcome.

SURVIVAL DATA – MEDICAL NOTES REVIEW (WEEK 28)

At week 28, medical notes review will be performed to collect survival data. Participants will not be required to attend the clinic nor they will be required to provide any data remotely.

WITHDRAWAL

A withdrawal form must be completed in the event of participant death or where the participants withdrew from the study and is no longer prepared to provide any follow up data. In the event a participant wishes to withdraw from further data collection, where possible, a withdrawal visits should be scheduled, either in person or remotely, to undertake a final set of outcome assessments. A withdrawal form must also be completed at week 28 when survival data is collected, if the participant completes the study to indicate that they did not withdraw from the trial.

6.6.4 IMPLEMENTATION OUTCOME

Details of implementation outcome can be found in Section 11. Embedded Process and Implementation Evaluation.

6.6.5 ADHERENCE TO DATA COLLECTION

Methods to reduce missing data:

- Training will be provided to all research staff to understand the risks to the integrity of the trial posed by missing data and methods to reduce missing data.
- Staff resource will be identified at each site to support data collection.
- The value of complete data collection and how to reduce missing data will be discussed with participants. During the informed consent processes, before they consent to enter the trial, potential participants will be supported to understand everything that will be required of them during the trial, including:
  - assessment visits and how long approximately the PROMs take to complete
  - why some questions are asked at each of the visits
  - that completing the PROMs in full at each visit provides us with the information we need to determine if and how the intervention is effective
  - that a member of their family or a member of the research team can help them fill in the PROMs, but that the answers should be their own opinion, and not those of their family or friends
  - that both arms are important to be able to answer the research question
  - details of what is involved in participating in the intervention, including that they can bring a member of their family or other person supporting their care, if they are allocated to the intervention arm.

To support participants to provide complete data, methods for PROMs collection will be flexible and tailored to participant's preference. These will include:

- Participant self-report returning the PROMs by email /or electronic transfer

- Participant completes PROMs individually or in presence of researcher (blinded to group allocation) in a setting of their choosing - health setting or their own home (where possible).
- PROMs completed by researcher entering responses provided by participant, either in the person's home (where possible) or a health setting, or remotely.

7. RECRUITMENT

7.1 ASSIGNING OF INTERVENTION

7.1.1 RANDOMISATION METHOD

Individual participants are allocated on a 1:1 basis to receive either palliative rehabilitation plus usual care or usual care. Treatment allocation will not be disclosed to the CTRU KCTU trial team or to other members of the research teams involved in data analysis to maintain blinding during outcome assessment and to minimise possible bias.

A computer-generated minimisation programme that incorporates a random element will be used to ensure that treatment groups are well balanced for:

- trial country
- baseline FACT-G score (<=64, 65-79, 80+)
- ECOG performance status (2, 3)

in order to guard against chance bias in patient allocation for prognostic factors.

7.1.2 BLINDING

Four data analysts will be blinded to group allocation.

Owing to the nature of the intervention, it is not possible to blind participants or intervention practitioners.

Individual blinding status	Blinded	Unblinded
Chief Investigator		X
Scientific Project Manager & Research Fellow		X
Principal Investigators and all other staff at site		X
Trial Manager/Trial Co-ordinators		X
Senior Trial Statistician	X*	
Trial Statistician		X
Trial Participants		X
Site research teams supporting assessment of outcomes data**	X	
Rehabilitation Practitioners		X
Trial Steering Committee (TSC)	X	
Data Monitoring Committee (DMC)		X

**Partially blinded*

***Country specific site research teams*

TABLE 2. BLINDING STATUS

The blinding status of the research team with respect to an individual participant's allocation is detailed in Table 2 above.

Senior Statistician will remain partially blinded to aggregated summaries by arm for Data Monitoring Committee reporting, and fully blinded each participant's treatment allocation until data lock and the commencement of the analysis. Local research team members supporting assessment of outcome data will be blinded. Rehabilitation practitioners (intervention providers) will remain fully unblinded as they do not support the assessment.

8. WITHDRAWAL OF PARTICIPANTS

All study procedures must be discontinued if:

- the participant decides they no longer wish to continue; or
- recommended by the principal investigator.

During site set up visits all research staff will be made aware of the risks to the integrity of the trial posed by missing data and how to reduce missing data. Research staff will understand that an excessive rate of withdrawals can render the trial uninterpretable; therefore, unnecessary withdrawal of participants should be avoided. Research teams at all sites will receive training on how to reduce missing data. Clinicians and healthcare professionals/research staff at sites and rehabilitation practitioners will be provided with training on how to minimise missing data during site initiation visits and training. This training will follow the principles in the PRincipleS for handling end-of-participation EVEnts in clinical trials REsearch (PeRSEVERE) guidance (Persevere Guidelines Website).

Participants in either the intervention arm or the control arm have the right to withdraw from the trial at any time if they no longer wish to continue.

The investigator also has the right to withdraw patients from the rehabilitation intervention in the event of inter-current illness, AEs, SAE's, protocol violations, administrative reasons or other reasons.

Should a patient decide to withdraw from the trial, they are not required to provide a reason, but they will be offered an opportunity to provide a reason. All efforts will be made to report the reason for withdrawal and reasons for missing data as thoroughly as possible.

Should a participant withdraw from receiving one or more of the three rehabilitation intervention sessions, in countries/regions where this is permitted, they will be offered the opportunity to continue to provide follow-up data AND/OR efforts will be made to continue to obtain follow-up data, with the permission of the participant.

Participants who withdraw from receiving the rehabilitation intervention or from the control arm will be asked, in countries/regions where this is permitted, to confirm whether they are still willing to provide any or all the following:

- all trial specific participant reported questionnaire data at weeks 4, 8 and 16
- FACT-G questionnaire data at 4, 8 and 16 weeks
- FACT-G questionnaire data at 8 weeks
- clinical data from medical records at weeks 4, 8, 16 and survival data at week 28 .

Participants in both arms who withdraw from all future trial related tasks, both intervention and data collection, will be asked if they are willing for data already provided, from consent to point of withdrawal, to be used in the trial analysis.

9. EMBEDDED EQUITY, ACCESS AND INCLUSIVITY EVALUATION

9.1 BACKGROUND & RATIONALE

Investigating how social inequality affects trial access and outcomes is important, hence we understand how social and psychological factors may affect trial enrolment and outcomes by exploring how age, gender, socio-economic position, cultural or personal beliefs, or comorbidities play a role in patient's engagement in the trial and trial outcomes. Not all patients report good experience from rehabilitation and palliative care, and access and equity challenges are apparent, e.g., according to diagnostic groups and tumour types. Inequality in health care applies especially to vulnerable groups of patients with multimorbidity, socioeconomic disparities or cultural and personal disadvantages. Determining equal

access and delivery of the intervention will enhance the future implementation of effective and equitable access to palliative rehabilitation into routine oncology and palliative care for people with incurable cancer, ensuring good outcomes for vulnerable patients.
Quantitative and qualitative survey and interview data will be collected and analysed, to identify potential mechanisms, mediators and moderators of access and treatment effect relating to person, intervention, and service characteristics. We will identify within- and cross-country barriers and facilitators to equitable access and delivery of the trial and intervention.

9.2 Social and Sociodemographic factors

The concepts of social and sociodemographic factors are measured at baseline by a mix of socio-demographic items from different studies: - gender, age, relationship status, living situation, having children, educational level, employment status, financial situation, geographical access to secondary health care, religious status, social support from family or friends, ongoing stressors, perceived discrimination by health care system and others, and health confidence (a broad concept encompassing aspects of self-efficacy, patient activation, health literacy, self-management, shared decision-making, capability, and empowerment)[52].

Data on ethnicity will only be collected in the UK.

9.3 Exploratory hypothesis testing and between country comparisons

For each of the primary and secondary effectiveness outcomes, exploratory hypotheses testing analyses will be performed using interaction terms added to its analysis model, to explore the extent to which the outcome differs by country, gender, social, clinical, and socioeconomic factors. Further exploration will be facilitated by incorporating into the models by how much the country-specific nature of usual care (e.g. levels of input to usual care from different professional groups) explains any observed outcome differences. Priority of interpretation will be given to the primary outcome, with secondary outcomes being supportive. Data analysis will be primarily descriptive with confidence intervals, given the number of analyses and the low statistical power.

9.4 Qualitative analyses

9.4.1 Patient perspectives

Deductive analyses will be informed by semantic information sought from two sources; transcriptions of the patient interviews (described in section 10.4.2) and the rehabilitation booklets. This will involve developing themes in advance of the analysis process and assessing the presence or absence of these themes across the data. Themes will cover aspects of access, inclusivity, and how personal or cultural beliefs affect engagement in the intervention and the participant's perception of a meaningful intervention.

9.4.2 Site specific strategies for equitable enrolment

Each study site involved in enrolment of patients will be asked to formulate a local strategy and action plan for an 'equitable inclusion into the study' using a template that will be provided.
The strategy will include a reflection on which groups of patients are recognised as potentially difficult to enrol based on experience from similar trials, how they will try and overcome the barriers, and which promoting factors are identified for an equitable inclusion.
Study sites will be encouraged to abide to the 2021 Equity and Inclusion Guiding Engagement Principles described by The Patient-Centered Outcomes Research Institute (ref. https://www.pcori.org/sites/default/files/Equity-and-Inclusion-Guiding-Engagement-Principles.pdf) and to involve local Public-Patient Involvement (PPI) groups and Patient Organisations where possible. Sites will be encouraged and supported to perform internal evaluations of their strategy and action plan every six months during the duration of the trial.

10. EMBEDDED PROCESS AND IMPLEMENTATION EVALUATION

10.1 BACKGROUND & RATIONALE

Understanding the degree to which an intervention is delivered and implemented as intended is essential to interpret trial results. Therefore, a robust implementation process evaluation, will be conducted to understand the complexity that arises both from the intervention's components and from its interaction within the context, and to identify if the findings can be confidently attributed to the intervention as delivered [53] .

Investigating the contextual factors of the intervention will provide an understanding if the intervention is acceptable, implementable, cost effective, scalable, and transferable across contexts [54]. This will maximize the impact of the intervention's scale-up in real-world settings. Combining effectiveness and implementation outcomes in the same trial avoids sequential findings and reduces the time of translation into routine practice. Moreover, it is a cost-effective approach.

The evaluation described here explores how the trial processes and intervention components were received and experienced by patients. An ancillary study will be set-up to investigate the contextual factors of the intervention realisation, and which challenges were faced by healthcare professionals by collecting their opinion and feedback.

A mixed methods approach will be used to collect data from patients before and following the delivery of the intervention[55]. Quantitative and qualitative designs will be used simultaneously for data' convergence and complementarity. Convergence will rely on a triangulation approach to assess the validity of the quantitative data by the qualitative data [56]. If discrepancies appear between the results emerging from qualitative data and those from quantitative data, we will apply the approach exposed by Moffatt et al [57]. Complementarity will be used to explore the experience of the intervention in depth [56].

Questionnaires and semi-structured interviews were designed in accordance with the new Medical Research Council framework for developing and evaluating complex interventions, determinants from the Consolidated Framework for Implementation Research [58], domains from the Theoretical Framework of Acceptability, [59] and Proctor's Implementation Outcomes Framework [60].

10.2 IMPLEMENTATION EVALUATION OBJECTIVES AND OUTCOMES

Proctor's implementation framework includes eight domains: acceptability, adoption, appropriateness, feasibility, fidelity, implementation cost, penetration and sustainability[60]. We will investigate domains relevant to the implementation context and intervention evaluated. These include acceptability as the perception of the intervention (agreeable, palatable, satisfactory), appropriateness as perceived fit/relevance of the intervention, and costs.

Intervention delivery processes (including number and duration of sessions completed, mode, location, participant goals and action plan, discreet intervention components, materials and equipment provided, onward referrals, participant receipt and enactment) will be documented by rehabilitation practitioners in the Data Collection Booklet.

Health care professionals' views on feasibility, fidelity and sustainability will be studied as part of an ancillary protocol. Adoption and penetration will not be investigated at this stage because they are not relevant in this specific clinical trial context, where no implementation strategy is being tested.

10.3 SELECTION OF PARTICIPANTS

All participants randomized in the intervention arm will be considered.

In the patient information sheet, implementation questionnaires and semi-structured interviews will be described, in addition to the rehabilitation process evaluation. Consent to the trial includes the quantitative

questionnaires. For the semi-structured interviews, patients will indicate their choice to be invited to participate with an optional box in the consent form.

10.4 ASSESSMENT SCHEDULE

Enrolled participants will be requested to respond to implementation questionnaires following randomisation to the intervention but before the first rehabilitation intervention session, and then at week 8, when the rehabilitation intervention is expected to be completed (see section 5.2.3).

Participants providing consent will be approached to review the information about the optional qualitative interview in the Participant Information Leaflet after completion and return of the week 8 questionnaire booklet. An interview will be scheduled with participants who provide informed consent, to be completed in the subsequent 1-2 weeks.

10.4.1 QUANTITATIVE ASSESSMENTS

Published quantitative questionnaires for each studied implementation items (https://implementationoutcomerepository.org/).

AIM

The Acceptability of Intervention Measure (AIM) [61] is a 4-item scale that measures the perception of satisfaction and agreeability of an intervention. Items are rated using a Likert-type semantic differential scale, ranging from 1 to 5. The AIM has a Cronbach's alpha of 0.85 [61].

IAM

The Intervention Appropriateness Measure (IAM), a 4-item scale measuring the perceived relevance and compatibility of the intervention. Items are rated using a Likert-type semantic differential scale, ranging from 1 to 5. The IAM has a Cronbach's alpha of 0.91 [61].

BESPOKE QUESTIONNAIRE

A bespoke quantitative questionnaires was designed using adapted items from our literature review of published implementation questionnaires (https://implementationoutcomerepository.org/), rated based on a semantic differential scale (Likert-type), to fit with the ratings used for AIM and IAM.

Sample size: Sample size calculation is not required for this part of the trial. We however plan for all patients randomized to the intervention arm to participate in the quantitative part of the implementation study, which represents around 170 patients (or fewer depending on numbers withdrawing from data collection).

Data Analysis:

Ordinal data will be described by with the frequency of the distribution and the median of the results. For descriptive data interpretation, the intervention will be considered to have good levels of acceptability and appropriateness if, for each question, the median score is ≥ 4 and if less than 30% of the individual median scores are ≤ 2. Conversely, if the median score is ≤ 2 and if less than 30% of the individual median scores are ≥ 4, the intervention will be considered to have low levels of acceptability and appropriateness. Other situations will be considered as inconclusive and the qualitative data will be prioritised for data interpretation.

Likert-type questions usually fall within the ordinal level of measurement which signifies that parametric analyses might not be appropriated [62]. However, for an adequate sample size (at least 5–10 observations per group) and if data can be considered as normally distributed (or nearly normal), parametric tests can be used with Likert scale ordinal data [63-65]. As using parametric tests is adequate for the expected sample size of 170 patients (fewer depending on numbers dropping out or not completing the intervention)., and to maximise the power of the tests, we will rely on parametric tests if our data distribution is confirmed as normal prior to data analysis. If the distribution does not follow a Gaussian distribution, then adequate non parametric tests will be used.

If parametric tests are used, we will use paired Student T-tests to compare the positions for each item, and the mean score of the AIM and IAM, before and after the intervention. ANOVAs (or Kruskal-Wallis H-tests if the sample size is not sufficient) will be used to compare the positions for each item, and for mean AIM and IAM scores, according to the efficacy of the intervention based on the FACT-G score. The IBM SPSS Statistics 21 software will be used for the implementation items statistics [66]. The significance level will be set at 5% (alpha 0.05). Interpretation will be made cautiously given the number of exploratory tests.

10.4.2 QUALITATIVE INTERVIEWS

Qualitative interviews will be conducted to assess the acceptability and the appropriateness of the intervention from the patients' point of view [55]. These will allow patients to offer their opinion and feelings about the intervention, to identify convergences and divergences between the quantitative and qualitative parts, and finally to deepen our implementation evaluation of the acceptability and appropriateness aspects.

The semi-structured interview topic guide has been developed by a stakeholders' committee . The topic guide will explore participant's experiences of the acceptability, appropriateness and accessibility of the rehabilitation intervention to address our research questions. The topic guide was developed in English and translated into the participant language using a process of forward-to-back translation to ensure homogeneity in data collection.

The interviews will be conducted individually for patients and scheduled to reduce additional demand and preferentially during hospital visits. The interviews will be performed in the participant's primary language by a researcher at the trial site. The interviews will be performed face to face when possible. If needed, they can be conducted remotely via videoconference. Interviews are expected to take between 30-60 minutes; the length of the interviews will be defined by the participant's health status, their comfort with this method, and the quantity of data they wish to provide. Researchers involved in interviews with the patients will be experienced in qualitative research and communication. In the event a participant experiences any difficulties during the interview, such as tiredness or distress, the interview will be halted and, if necessary, ended.

The interviews will be tape-recorded and stored on a secure computer at the inclusion site. There will be two copies of the record on the computer: a master copy and a workable copy. The records will be transcribed, encrypted and stored in the participant language. While transcribing the data, researchers will remove any names and other identifiable information. In all participating centres, the recordings will be transcribed in-house by and authorised researcher. The recordings will be processed and stored in a GDPR compliant manner using appropriate technical and organizational measures to maintain a high level of security, including encryption, system resilience, and regular testing. Names and any other identifiable data will be removed before transcribing. Once transcription is complete, the researcher will go through the transcription and recording a second time for quality assurance to ensure that the entire recording has been copied and is clear. The records will be deleted off the server permanently after data analysis has been completed.

Sample size: The sampling will aim to represent different situations in balanced ratios. Participants that can provide various expertise, experiences and opinion on the intervention will be included to emphasise the generalizability of our qualitative results [56]. It is expected that between two to four participants from each country will be sufficient to inform our research objective.

Participants will be interviewed in their own language by a researcher at the inclusion site after completing the rehabilitations intervention and their consent obtained. Participants that have decided to withdraw from the trial will also be invited to take part in the qualitative interviews.

Data analysis:

The data analysis will rely on a reflexive thematic analysis using a basic semantic coding [67, 68].

Two researchers from the inclusion site will independently read the whole dataset twice to familiarize with the data. Then, they will generate initial codes (in English) corresponding to conceptual categories identified through verbatim and using the NVivo software.

Each trial site will discuss and refine codes, themes and sub themes. After coding each interview, researchers at each inclusion site will send a list of distinct themes, with accompanying quotes, to the implementation evaluation lead for an overall mapping of the themes and for a theorisation. As a wider group, the investigators will discuss the different themes to identify those that are shared between all inclusion sites or those that, conversely, are particularly discordant where relevant.

Codes will be categorised into themes and sub themes to create a working analytical framework which will represent semantic groups of concepts. All themes in the working analytical framework will be clearly defined. Analyses of the qualitative data will be performed simultaneously at each inclusion site using thematic analysis and framework analysis. Using the framework, researchers will code the remaining transcripts in NVivo and will review the coding frame until no additional codes emerge. Data will be summarised by category and chart the summary into a matrix. The data will be interpreted by exploring convergence and complementarity with quantitative assessments. Findings will be presented in a final framework/matrix.

11. DATA MANAGEMENT

There are three datasets in the trial: the KCTU randomisation dataset and two KCTU Ennov Macro eCRF system dataset. The CI will act as custodian for the trial data.

Source data worksheets will be supplied to all recruiting sites by the co-ordinating centre for the region. These will be prepared after the database specification is finalised and database testing is complete. The UK Trial Manager will send the master version to the co-ordinating teams in other European centres who will be responsible for adding validated version of country-specific participant-reported outcome measures in local languages.

Data will be transcribed from the source to the MACRO eCRF system, ideally within 7 days of the study visit. Participating sites will complete source data location lists defining the source data at their site.

11.1 RANDOMISATION SYSTEM AND MACRO EDC

Two web based electronic data capture (EDC) systems will be designed, using the InferMed Macro system. The EDCs will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. Both EDCs will be hosted on a dedicated server within KCL (see section 6.4 Data Entry for additional information).

A web-based randomisation system will be designed, using the bespoke KCTU randomisation system. The randomisation system will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL.

Randomisation will be at the level of the individual using the method of minimisation balancing the factors of the trial participant's country, baseline FACT-G score (<=64, 65-79, 80+) and ECOG performance status (2, 3) to guard against chance bias in patient allocation for prognostic factors. Individual participants are allocated on a 1:1 basis to receive either rehabilitation plus usual care or usual care only.

Please see section 6.4 Data Entry for additional information.

11.2 SECURITY

The CI or delegate (e.g. Trial Manager) will request usernames and passwords from the KCTU. Database access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the EDC and randomisation system are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g. Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g. Trial Manager) in the first instance.

Participant initials (in countries where this is permitted) and year of birth will be entered on the EDC and Randomisation system. Whereas NHS number (in the UK) or its equivalent, telephone number, email addresses, participant names and addresses, and full postcodes will not be entered into the EDC and Randomisation system. No data will be entered onto the EDC and Randomisation system unless a participant has signed a consent form to participate in the trial.

11.3 DATA QUALITY PROCESSES

At the database design stage, validations will be programmed into the systems to minimise data entry errors by querying the data entered in real time with sites.

The CI and central team will undertake appropriate reviews of the entered data, in consultation with the project analyst where appropriate for the purpose of data cleaning and will request amendments as required. No data will be amended independently of the study site responsible for entering the data.

No data can be amended in the randomisation system, however CI or delegate (e.g., Trial Manager) may request King's Clinical Trials Unit to add notes against individual participant entries to clarify data entry errors. Any errors should be reported by site staff to the Trial Manager as soon as possible once they are detected. The trial manager will onward report errors to KCTU and retain records in the TMF.

The KCTU will provide the Trial Manager with Data Management Plans for both the Ennov Macro eCRF and the randomisation system once the systems are made live. Those documents will be filed in the Trial Master File.

A regular Data Management Report will be produced by KCTU and passed to the Trial Manager, who will raise Data Clarification Requests (DCRs) with sites in the MACRO eCRF system. Study sites will periodically review raised DCR's and respond to the queries raised.

Queries will be raised with sites during the monitoring visits.

11.4 DATABASE LOCK

At the end of the trial, the site PI will review all the data for each participant and provide electronic sign-off to verify that all the data are complete and correct. At this point, all data can be formally locked for analysis.

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will distribute onward as appropriate.

12. STATISTICAL METHODS

12.1 SAMPLE SIZE JUSTIFICATION

Before considering dropout, a sample size of 238 (119 per arm) would provide 90% power at the 2-sided 5% significance level to detect a 5.5-point difference in the mean 8-week FACT-G between arms, adjusting for baseline FACT-G, using analysis of covariance (ANCOVA) or equivalently using the linear mixed effects model planned for the primary analysis This assumes a standard deviation (SD) of 13, based on an estimated residual SD of 13.05 from an ANCOVA of the baseline and arm adjusted outcome in the feasibility trial [29], supported by estimated SD of 12.4 for the change from baseline in a relevant trial [69]. The detectable difference is based on a minimally important difference for FACT-G of 5-6 points derived from multiple approaches and datasets in the relevant population [70]. In order to allow for up to 30% dropout, a sample size of 340 (170 per arm) randomised participants is planned. As the linear mixed effects model makes a missing at random assumption utilising the FACT-G at other timepoints, it is expected that the precision of the estimated intervention effect will be increased in comparison with ANCOVA.

12.2 STATISTICAL ANALYSIS

12.2.1 STATISTICAL METHODS FOR PRIMARY OUTCOME

The primary outcome analysis approach is informed by guidance on estimands and sensitivity analyses [71]. The relevant study objective is to assess the improvement in quality of life from introducing an integrated short-term palliative rehabilitation for those with incurable cancer. The intention to treat (ITT) population comprises those participants randomised into the trial. They are retained in their randomised arm for the purpose of analysis. The primary outcome is the FACT-G measured 8-weeks after randomisation. There are additional baseline, 4-week and 16-week FACT-G measurements. Principal post-randomisation ("intercurrent") events to consider are the discontinuation of the intervention without having made an action plan in the first meeting, and the death of the participant before an 8-week FACT-G can be provided (Table 3 below). The population-level summary measure is the absolute difference in population mean 8-week FACT-G between the intervention and comparator arms.

The primary analysis approach will be in the ITT population and will have two parts. Part 1 will involve a linear mixed effects model (LME), involving the correlated 4-week, 8-week and 16-week FACT-G as the outcomes, allowing different correlations between pairs of FACT-G measurements to be reflected in the model. The covariates will be the arm, the continuous FACT-G at baseline (linear term), ECOG (categorical), and country (categorical). The post-randomisation timepoint (categorical) will also be included as a main effect term and in interaction with each covariate. This model is therefore very similar (in terms of inference and power) to a corresponding Analysis of Covariance (ANCOVA) model but utilises other timepoints to therefore make a more plausible Missing At Random (MAR) assumption than that of the ANCOVA model. Part 1 provides an estimate with 95% Confidence Interval (CI) for the 8-week FACT-G intervention effect.

Unlike the Part 1 model, Part 2 does not exclude participants who have no post-randomisation FACT-G data, classifying the two-part analysis approach as an ITT strategy. Part 2 is a sensitivity analysis which challenges the plausibility of the MAR assumption and tests the robustness of the Part 1 findings. The method applies a range of possible values (in size and direction relatively favourable and unfavourable for the intervention) for the unknown excess absolute intervention effect in 8-week FACT-G non-responders relative to the Part 1 intervention effect, as used previously [72]. This provides a series of potential intervention effects with 95% CIs that reveal the degree of robustness to departures from the Part 1 MAR assumption. The model will also provide the estimated intervention effect and 95% CI for the 4-week and

16-week FACT-G. Similarly, a LME model will be used to analyse each secondary repeated-measures outcome variable.

The intercurrent event of not complying to produce an action plan is ignored in the primary outcome analysis approach above due to the emphasis on the ITT approach which takes a treatment policy strategy for this event and accepts all FACT-G outcomes into the analysis to answer the scientific question, pragmatically accepting the influence on these from reduced intervention compliance. The event will however be examined with the Complier Average Causal Effects (CACE) method, in those confirmed eligible, which will provide an estimate with 95% CI of the primary outcome intervention effect in those complying in making an action plan and their comparator arm counterparts, as used previously [73]. Assumptions with the methods (LME, CACE) will be assessed, and the methods and alternatives for these will be detailed in the statistical analysis plan. Discontinuation of randomised intervention can arise for several alternative reasons which may be recorded. Part 2 of the primary outcome approach already examines overall robustness to missing data, whether or not from study withdrawal or death. The intercurrent event of death is important to consider in palliative and end-of-life trials [74]. Deaths are expected to be relatively rare in the initial weeks after randomisation due to the eligibility criteria, and rarer still within the ECOG 2 stratum. The intervention is not expected to affect timing of death. Death of a participant in either arm may occur before the primary outcome is provided at its intended collection point by the 8-week +3-day window point, and a 4-week FACT-G may have been provided. Sensitivity analysis will be considered, for these participants, where (i) the 4-week FACT-G is taken to fully represent such a participant's end-of-life period, and is replaced as the 8-week outcome and/or (ii) those who have died are prevented from the primary outcome model's implicit 8-week FACT-G imputation after death, by removal of the 4-week outcome data. These contrast the Part 1 analysis, which implicitly imputes FACT-G after the death of a participant for any cause, just as it will after withdrawal or other missing data in the follow-up timepoints, reflecting a "hypothetical strategy".

Population of interest (common to the 3 timepoints)	All trial participants eligible at baseline		
Variable (endpoint) of interest	FACT-G at 4 weeks	FACT-G at 8 weeks (Primary Outcome)	FACT-G at 16 weeks
Treatment of interest (common to the 3 timepoints)	Three rehabilitation intervention sessions with a rehabilitation practitioner		
Intercurrent events:	**Strategies for addressing the intercurrent events:**		
Death	Hypothetical	Hypothetical	Hypothetical
Disease deterioration/progression	Treatment policy	Treatment policy	Treatment policy
Palliative rehabilitation discontinuation (Failure to make an Action Plan in the first palliative rehabilitation intervention visit)	Treatment policy	Treatment policy	Treatment policy
Palliative rehabilitation discontinuation due to an AE either related or unrelated to the intervention	Treatment policy	Treatment policy	Treatment policy
Start of another rehabilitation programme*	Treatment policy	Treatment policy	Treatment policy

Population-level summary for the variable:	Difference in FACT-G means between those receiving palliative rehabilitation plus usual care or usual care only at 4 weeks	Difference in FACT-G means between those receiving palliative rehabilitation plus usual care or usual care only at 8 weeks	Difference in FACT-G means between those receiving palliative rehabilitation plus usual care or usual care only at 16 weeks
Analysis method:	LME with additional analyses as described above	LME with additional analyses as described above	LME with additional analyses as described above

**This would be equivalent to a 'rescue medication' therapy in Investigational Medicinal Product trials*

TABLE 3. ESTIMANDS ATTRIBUTES

12.2.2 STATISTICAL METHODS FOR SECONDARY OUTCOMES

The detailed statistical analysis plan will include further details of the statistical methods to be used for secondary outcomes.

12.2.3 STATISTICAL METHODS FOR ADDITIONAL ANALYSES (E.G. SUBGROUP ANALYSES)

The consistency of the primary outcome result will be examined across categories of subgroup variables. These will be listed in the statistical analysis plan, and will include gender, age, diagnosis (locally advanced or metastatic disease), ECOG performance status and country. The LME model will be extended to include 2-way interactions between trial arm and subgroup variables. Effect sizes with 95% confidence intervals for each prognostic group including, gender, age, diagnosis (locally advanced or metastatic disease), ECOG performance status, country and other factors will be estimated. These analyses have relatively high variability to be able to make statistically robust conclusions, therefore caution will be exercised in the reporting and interpretation of the estimates and 95% confidence intervals obtained from these analyses.

Exploratory predictive analyses are planned to investigate if participants derive a different level of benefit from palliative rehabilitation with respect to the primary outcome, FACT-G, and the global disability WHODAS score based on baseline socio-demographic or clinical characteristics.

Safety analyses will summarise the number and characteristics of adverse event rates (determined by routine clinical assessments). Safety data will be presented using populations according to the treatment received.

12.2.4 STATISTICAL ANALYSIS PLAN

A full statistical analysis plan (SAP) will be drafted in accordance with the KCTU Standard Operating Procedures authored and approved by the Senior Trial Statistician, and approved by the Trial Steering Committee (TSC) and Data Monitoring Committee (DMC). Amendments to the SAP made during the trial after the point of the DMC seeing outcome summaries, and up to the data lock, will be re-approved by the TSC only.

The trial statistician will be fully unblinded to be able to produce regular reports for the DMC during the trial. The senior trial statistician will be prevented from knowing which arm each participant is in up to the data lock and will supervise the production of open and closed DMC reports which will not reveal which arm is which.

The Trial Statistician will not take part in any discussion that influences the early stopping of the trial at any TMG or TSC meetings.

12.3 Interim Analyses

There are no planned interim analyses.

12.4 Methods to Achieve Target Sample Size

Trial recruitment will be monitored closely by the Trial Manager and reported at the TMG meetings. Pseudo-anonymised participant pre-screening logs will be requested from sites and assessed on an ongoing basis. Section 4.2 outlines how participants will be identified for inclusion in the trial.

Additionally, the KCTU Standard Operating Procedures (SOPs) will guide the trial statistician's reports outlining recruitment numbers across the trial and at site level to the DMC. The DMC will be asked to advise on strategy where there are recruitment difficulties i.e., including but not limited to; modifications to the inclusion/exclusion criteria, targeted recruitment drives, escalation at site level to PI/R&D or site closure.

12.5 Methods to Handle Missing Data

All participants who are randomised and have at least one follow-up time point will be analysed as per their allocation group (intention-to-treat) for the primary outcome in the first part of the primary outcome analysis. In the second of the two-part analysis approach, all randomised participants will be included as per their allocated group. Missing data at baseline in the effectiveness analysis will be handled using the missing indicator method.

In the health economics analysis, although baseline data should be complete prior to randomisation, there may be some limited missing data. Descriptive baseline summaries will be presented as complete case. The proportion of missing data will be summarised by scale/assessment. Methods for handling missing health economic analysis data will be implemented according to previously described methods [75].

12.6 Methods to Handle Compliance

Compliance will be defined in the SAP, drawing on CACE analysis within section 14.2.1, and Section 5.4 Adherence to the trial intervention for more details.

12.7 Plans to Give Access to the Full Protocol and Participant-Level Data

It is anticipated the full protocol and all results will be available as open access according to the funding bodies publication policies.

13. Measurement of Costs and Outcomes

13.1.1 Health economic assessment

We will estimate costs and effects on quality of life of patients in each arm of the trial; we will then summarize cost-effectiveness and cost-utility of the intervention using cost-effectiveness planes.

Resource utilisation will be measured using medical records and Client Service Receipt Inventory (CSRI) questionnaire, a validated and widely used instrument, useful for measuring possible differences in resources usage between arms. Furthermore, cost vectors for these resources will be estimated for each participating country; unit costs for different countries/years will be normalised using inflation indices per

country (regarding time, where needed) and purchasing power parity adjustments (regarding countries). The costs will be evaluated considering both a health sector and a societal point of view; in this latter evaluation, which has to be considered the main one, costs for caregiver/families/informal care provided to patients will be counted as well.

Effects of the intervention will be measured by FACT-G. Both a cost-effectiveness (CEA) and a cost-utility analyses (CUA) will be performed: in order to ensure comparability with other programs (not necessarily using FACT-G as effectiveness outcome), CUA will be considered the primary economic analyses. FACT-G QOL will be mapped to utilities using the equations developed by Meregaglia et al [76]; QALY will then be estimated using area under the curve method.

Costs and effects will be monitored and compared up to 16 weeks from randomisation; given this time horizon no discount rate will be applied (discount rate = 0).

The main analysis will be a cost-utility evaluation, from a societal point of view, using cost-effectiveness plane and handling uncertainty by bootstrap replicates [77]; probability of cost-effectiveness of the intervention will be studied according to different willingness to pay (WTP) thresholds per QALY. Whether no differences in effectiveness should be found (bootstrap replicates on y-axis), the probability of cost-effectiveness will be an approximate constant (for several WTP) estimate of probability of the intervention to be less costly.

The full-analysis performed (including further sensitivity analyses and missing data handling) will be detailed in a Health Economics Analysis Plan (HEAP), currently in development according to international guidelines [78-80], which will be released before database lock as project deliverable.

14. Adverse Events Management and Reporting

Adverse Event (AE): is any untoward medical occurrence in a study participant including occurrences which do not necessarily have a causal relationship with the study intervention (e.g. unfavourable symptoms or disease).

Serious Adverse Event (SAE): is any untoward event or omission that has given rise to, or has the potential to give rise to, undesirable effects that may cause serious harm to an individual. Serious adverse events additionally result in one or more of the following:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect; or
- is otherwise considered medically significant by the Principal Investigator or delegate.

14.1 Recording and Reporting of Adverse Events

The safety reporting guidance in Appendix 1 will be followed alongside the below:

All adverse events will be recorded from consent to the end of study visits in the participants medical notes, the study source data worksheets and the eCRF. SAE's will be additionally reported, within 24 hours of site becoming aware of the event to the Sponsor and the CI.

All SAEs (except those specified in this protocol as not requiring reporting) will be reported immediately (and certainly no later than 24 hours) by the Investigator to the CI for review in accordance with the current REC SOP (https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/research-ethics-

committee-standard-operating-procedures/). The Chief Investigator is then responsible for reporting events to the Sponsor.

All adverse events will be assessed and categorised for severity, causality and expectedness as described below. The assessment of relationship of adverse events to the intervention and their expectedness are a clinical decision based on all available information at the time of the completion of the adverse events reporting. All adverse events will be documented in the trial Data Collection Booklet for practitioners, as well as recorded on the eCRF.

All SAEs, (except those specified in this protocol as not requiring reporting) should be reported immediately to the Chief Investigator and to the Sponsor.

The Chief Investigator and regional Programme Leads will report within 15 days of becoming aware of the event to relevant ethics committees in the UK (REC) and in Europe, if in the opinion of the Chief Investigator (CI) the event was:

- Related – that is, it resulted from administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

In the UK, reports of related and unexpected SAEs will be submitted to the REC using the Non-CTIMP safety report to REC form available on HRA website: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/. The form will be completed in typescript and signed by the Chief Investigator. The main REC will acknowledge receipt of safety reports within 30 days. A copy of the SAE notification and acknowledgement receipt will also be sent to the Sponsor.

Where an SAE occurs that does not require immediate reporting, this SAE should be reported in the Annual Progress Report and copied to the Sponsor, alongside any AEs that occur that are not classified as 'serious'.

All adverse events that are to be reported to the Sponsor must be signed and dated and completed by the Chief Investigator (N.B. Data breaches are also classified as SAEs).

14.2 Evaluating of AEs and SAEs

14.2.1 Assessment of Severity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the Investigator's clinical judgement. The intensity of each AE and SAE recorded in the eCRF should be assigned to one of the following categories:

- **Mild** - The adverse event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort
- **Moderate** - The adverse event interferes with some aspects of the participant's routine, or requires further procedure, 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

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

14.2.2 Assessment of Causality

The Principal Investigator is obligated to assess the relationship between intervention and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the intervention will be considered and investigated.

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

- **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.

There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always assesses causality for every event prior to transmission of the SAE form to the Sponsor. The Investigator may change his/her opinion of causality considering follow-up information, amending the SAE form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

14.2.3 Assessment of Expectedness

A reasonable possibility of a relationship conveys that there are facts, evidence and/or arguments to suggest a causal relationship, rather than a relationship that cannot be ruled out.

The following events will be classified as expected **adverse events:**

- Expected: an adverse reaction, the nature of which is consistent The following with the following events:
    - deterioration related to underlying cancer diagnosis
    - 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.
    - symptoms relating to underlying cancer or co-morbid condition, including breathlessness, fatigue, cough, insomnia, anxiety, depression
- Unexpected: an adverse reaction related to any other occurrences than those listed above, including adverse events that become more frequently reported or more severe than previously reported (e.g. increased frequency of falls, worsening fatigue or acute worsening of breathlessness).

14.3 Serious adverse events that do not require reporting in the INSPIRE Trial

The following events, occurring following randomisation until 30 days post final rehabilitation intervention session, will not be classed as SAEs within this trial and will therefore not be subject to expedited reporting (they will still need to be reported to KCTU e.g. death reported on the CRF):

- Death as a result of cancer disease progression.
- Hospitalisation or admission into a hospice, nursing home or palliative care unit due to caregiver burden;
- Expected deterioration related to underlying cancer diagnosis;
- Routine treatment of any known comorbid conditions not associated with any deterioration in condition;
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications;

- Any admission to hospital or other institution for general care where there was no deterioration in condition;
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

14.4 Stopping Rules

The trial may be prematurely discontinued by the Sponsor or Chief Investigator on the basis of new safety information or for other reasons given by the Data Monitoring Committee / Trial Steering Committee regulatory authority or ethics committee concerned.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from a Trial Steering Committee (if applicable), who will advise on whether to continue or discontinue the trial and make a recommendation to the sponsor. If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collect

15. Oversight and Monitoring

15.1 Roles and responsibilities of the Study management Committees, Groups & Individuals

15.1.1 Trial Management Group (TMG)

Position	Name	Organisation	Role
Chief Investigator	Matthew Maddocks	KCL	Chair
Scientific Manager	Joanne Bayly	KCL	Member
Senior Statistician	Toby Prevost	KCL	Member
Statistician	Joana Carvalho Vasconcelos	KCL	Member
Senior Trial Manager	Sylvia Wilczynska	KCL	Member
Clinical Academic Project Lead	Barry Laird	UoE	Member
Project Manager (Reggio Emilia-IT)	Elena Turola	AUSL-IRCCS RE	Member
Site Investigator (Reggio Emilia – IT)	Stefania Costi	AUSL-IRCCS RE	Member
Patient representative	Juan-Jose Ventura	ECPC	Member
Project Lead	Mai-Britt Guldin	FAP	Member
Clinical Academic Project Lead	Guillaume Economos	HCL	Member
Trial Manager	Anne-Sophie Belmont	HCL	Member
Ph.D student	Julia Romeyer	HCL	Member
Site Investigator	Elisa Vanzulli	INT	Member

Site Investigator	Maria Grazia Blandini	INT	Member
Project Lead	Line Oldervoll	UiB	Member
Academic Project Lead	Guro Stene	UiB	Member
Project Manager	Lise Nottelmann	FAP	Member

TABLE 4. TRIAL MANAGEMENT GROUP MEMBERSHIP IN Inspire

Members of the TMG are listed in Table 4 above. Changes in individuals filling these roles will not require a protocol update but will be documented in the TMG minutes. The TMG will be responsible for the general oversight of the trial.

15.1.2 TRIAL STEERING COMMITTEE (TSC)

The TSC is an executive committee, reporting to the Sponsor. The TSC will provide overall independent supervision of the trial, monitor trial progress and conduct and provide public/service user, clinical and professional advice relating to the trial design. The TSC will consist of the following 6 voting members, with representative from different countries: Chair, Vice Chair, members with trial and clinical discipline experience (e.g. clinicians with research experience, methodologists, critical friends), Statistician, Patient Representatives. Independent members will be independent of the Sponsor organisation and of any recruiting study sites. Final agreement of membership will be made by the TSC itself at the initial meeting. The first TSC meeting will be held as a joint meeting with the DMC to facilitate the agreement of roles and responsibilities, lines of communication, review of the protocol and the timing of future meetings. Future meetings will be agreed and specified in the TSC Terms of Reference and timed to facilitate timely review of DMC recommendations.

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Data Monitoring Committee, Trial Steering Committee, regulatory authority or ethics committee.

If the trial is prematurely discontinued, active participants will be informed, and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

15.1.3 DATA MONITORING COMMITTEE (DMC)

The DMC will consist of 3 independent voting members: a statistician and two clinicians. Members will be independent of the Sponsor organisations and of any recruiting study sites. The DMC is an advisory committee reporting to the TSC. The DMC's role is to monitor the safety, data and related ethics of the trial and to provide independent advice and recommendation on all matters that impact ethical considerations, based on relevant clinical and professional expertise. The first DMC meeting will take place prior to recruitment for the trial as a joint meeting with the TSC. Future meetings will be held as specified in the DMC charter. The DMC will work to the DAMOCLES guidance [81].

15.1.4 PRINCIPAL INVESTIGATOR (PI)

The PI who is registered on the site delegation log, is responsible for:

1. Using judgement in assigning seriousness, causality and if requested whether the event was anticipated using the expectedness information approved for the trial (as detailed in Section 14).
2. Ensuring that all reportable SAEs are recorded and reported to the Chief Investigator and the Trial Manager immediately, or at a least within 24 hours, of becoming aware of the event and provide

further follow-up information as soon as available. Ensuring that SAEs are chased with the Trial Manager if a record of receipt is not received within 1 working day of initial reporting.
3. Ensuring that AEs are recorded on the participants medical notes, the study source data worksheets and the eCRF.
4. Ensuring the completeness of eCRF before signing off at the end of study

15.1.5 CHIEF INVESTIGATOR (CI) / DELEGATE

The CI or delegated individual is responsible for:

1. Oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using judgement in assigning the SAEs seriousness, causality and whether if requested, the event was anticipated (in line with the expectedness information) where it is required as a second clinical opinion or if it has not been possible to obtain local medical assessment.
3. Using judgement in assigning whether the event was anticipated using the expectedness information approved for the trial (as detailed in Section 14).
4. Immediate review of all Related and Unexpected SAEs.

15.2 ROLE OF SPONSOR

The sponsor, King's College London (KCL), will take primary responsibility for ensuring that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting. KCL takes responsibility for arranging the initiation and management of this research, and for ensuring that appropriate standards, conduct and reporting are adhered to regarding its facilities and staff involved with the project.

A National Coordinating Centre will be identified for each participating country. Collaboration agreements will be signed between KCL and Hospices Civils de Lyon (HCL) who will oversee contracts and other legal processes in the recruitment sites in France and Italy. Collaboration agreements will be also signed between KCL and partners in Denmark and Norway who oversee contracts and other legal processes in the recruitment sites in their countries.

15.3 MONITORING

Monitoring of this trial to ensure compliance with Good Clinical Practice and scientific integrity will be managed centrally by the KCTU Trial Manager.
The trial manager will prepare a monitoring plan in accordance with local regulatory and REC requirements. At the site initiation visit, the Trial Manager will provide the recruiting site with an Investigator Stie File to be maintained for the duration of the study.

16. ETHICS & REGULATORY APPROVALS

Ethical and regulatory approval will be sought in each participating country. The UK Trial Manager will be responsible for authorising the submission packs for regulatory and ethics approvals in the UK and the EU countries. Each participating country will be responsible for local ethics and regulatory submissions.

Individual participants will consent to participate. The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996) [82] the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the UK Policy Framework for Health and Social Care Research [83] and the Mental Capacity Act 2005 [84].

This protocol and related documents will be submitted for review to Health Research Authority (HRA) [name after submission], Research Ethics Committee (REC) [name after submission]. All correspondence with the REC and HRA will be retained.

The Chief Investigator will submit a final report at conclusion of the trial to the funder, the REC and the Sponsor.

16.1 Protocol Amendments and Version Control of Study Documents

The UK Trial Manager, in agreement with the Sponsor, will be responsible for preparing and submitting protocol amendments to the ethics committee in the UK. Relevant documentation will be passed to the co-ordinating team in the EU countries to submit and disseminate locally.

Country-specific participant-facing documents (e.g participant information sheet, consent form, participant rehabilitation action plan (intervention group only) will be adjusted by the co-ordinating centre in each country and the co-ordinating centres are responsible for maintaining version control and track-changes copies and ensuring the documents contain all relevant information to meet local regulatory requirements.

Substantial amendments that require review by the REC will not be implemented until that review has been completed with a favourable outcome, and other mechanisms are in place to implement at site.

Once approved by ethics and regulatory bodies in the relevant country, the documents will be sent to site by the co-ordinating team in that country for filing in the Investigator Site File and acknowledgement will be requested and retained from each site. All correspondence, including submission packs with attachments and approvals, will be forwarded to the UK Trial Manager for filing in the global Trial Master File. Site staff CVs, GCP certification and delegation logs will also be retained in the global Trial Master File at KCL.

Recruiting study sites are responsible for communicating relevant information to participants.

The UK Trial Manager will be responsible for updating the ISRCTN register subsequent to relevant protocol amendments.

16.2 End of Study reporting

16.2.1 End of study declaration

The end of the study will be declared to the REC that gave a favourable opinion (as per the above Regulatory Approvals section) within 90 days of the study ending.

16.2.2 End of study reporting

The end of the study report will be submitted to the REC that gave a favourable opinion (as per the above Regulatory Approvals section) within 12 months of the study ending.

17. Miscellaneous

17.1 Plans for Independent Audit

There are no current plans to commission an independent audit study.

17.2 Confidentiality

When consent forms are signed, a copy will be provided to the participant, a copy will be filed in the medical records and the original will be retained in the Investigator Site File. Participant initials (in countries where this is permitted) and year of birth will be entered into the study database, but no more identifying information will be collected outside of the recruiting study site. Within site, an Investigator Site File will be maintained by the site PI. Participants will be fully identifiable within these files.

The patients' identifiable data will be kept for 15 years after the study has finished.

When the study is complete, a data sharing dataset will be created from the raw data by the study analyst, which will not include participant initials, year of birth or any other identifiable data and study PIN will be altered so that individuals are not recognisable from the dataset.

The study will comply with the General Data Protection Regulations (GDPR) relying on the 'public task' grounds as the lawful bases for processing personal data, and its UK implementation, Data Protection Act (DPA) 2018 [ref].

17.3 DEVIATIONS AND SERIOUS BREACHES

The KCTU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to promptly notify the Sponsor and to the regulatory authorities of a serious protocol deviation/violation and a serious breach (as defined in Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments) that they become aware of.

17.3.1 SERIOUS BREACHES

A 'serious breach' is a breach which is likely to effect to a significant degree: –

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial. In the event of doubt or for further information, the Investigator should contact the Sponsor.

17.3.2 PROTOCOL COMPLIANCE

A protocol deviation is any non-compliance with the trial protocol, GCP, or Manual of procedure requirements. Any deviation occurring at sites should be reported to the CI and the Trial Manager, and the Sponsor immediately. As a result of deviations, the Trial Manager will advise and/or undertake any corrective and preventative actions as appropriate. The protocol non-compliance will be recorded on the Protocol Deviation Log and retained in the global Trial Master File.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

17.4 DISSEMINATION PLANS

Early and open sharing of this research will be facilitated through use of protocol registration, pre-prints, and open access to publications and data.

Protocol registration: The trial protocol will be prospectively registered with ISRCTN.

Pre-prints: Manuscripts describing the findings of the trial, process and implementation evaluation and an equity and inclusivity evaluation will be uploaded to the medRxiv.org pre- print server prior to or alongside submission to academic journals, to ensure early open access to findings and opportunities for additional feedback.

Open access publications: Findings of the trial, process and implementation evaluation and an equity and inclusivity evaluation will be published in peer-reviewed journals with open access, in line with King's College London's Research Publications Policy. This policy recognises that open access provides greater visibility of research worldwide, supports research collaborations, and ensures reach to the widest possible audience. All publications will also be deposited in the King's College London PURE repository for scientific publications, with immediate open access.

Data sharing: In line with the King's College London Data Management Policy and Procedures and Horizon Europe open science practices, we will ensure our research data is as open as possible and as closed as necessary. This will be facilitated through use of the King's Open Research Data System (KORDS): an institutional research data repository which adopts the FAIR guiding principles and includes detailed.

Social media accounts (Twitter and LinkedIn) and the project website (https://palliativeprojects.eu/inspire/) provide opportunities for rapid dissemination of research findings and key messages, linking INSPIRE with the wider network of relevant stakeholders; individual and institutional.

The EAPC World Congress (3000+ delegates) and the EAPC World Research Congress (1000+ delegates) take place on alternate years. These and other targeted congresses will provide opportunities to showcase latest research findings. Additionally EAPC will provide ongoing knowledge exchange between other relevant EU project groups conducting research in related areas through:

- Joint networking events for researchers of EU-funded projects at the EAPC Annual congress
- Supporting engagement of junior project researchers in the EAPC Research Network Junior Forum
- Involvement of project principal investigator in the EAPC EU Projects Task Force.

17.5 END OF TRIAL

The end of the trial will be defined as database lock.

17.6 COVID-19 CONTINGENCIES

The COVID pandemic has impacted clinical trial work. Some of the visits, such as baseline and intervention rehabilitation visits will be conducted face-to-face. If face-to-face visit is not possible, 2nd and 3rd rehabilitation visits can be conducted remotely or, where possible, can be safely arranged at the participant home. Face-to-face visit is essential for baseline and the 1st intervention rehabilitation visit and where permitted will be conducted with full Personal Protective Equipment (PPE) and infection control procedures as required by the study sites.

17.7 AVAILABILITY OF DATA AND MATERIALS

De-identified data will be available for sharing upon request for future scientific research, subject to approval by the Chief Investigator. This may involve data being transferred outside the UK and to commercial partners and/or vendors for the purposes of research.

17.8 FUNDING

Funding to conduct the trial in the European Union is provided by HORIZON-HLTH-2021-DISEASE-04. In the UK this study is funded by UKRI Innovate (UKRI Reference Number: 10047799).

17.9 INSURANCE AND INDEMNITY

The study is sponsored by King's College London (KCL). The Sponsor will, at all times, maintain adequate insurance in relation to the trial: KCL through its own professional indemnity (Clinical Trials) & no-fault compensation, in respect of any claims arising as a result of negligence by its employees, brought by or on

behalf of a trial participant. KCL provides no fault liability insurance in the event of harm arising from the study design.

National Coordinating Centres (NCCs) in the participating countries across Europe are responsible to take out and maintain sufficient and appropriate clinical trial insurance and to provide indemnity in the event of clinical negligence in accordance with and to the extent required in the applicable laws and regulations in relevant region.

NHS staff (including honorary contract holders) undertaking research as part of their job role are covered by NHS Resolution indemnity schemes if working for a member of those schemes, subject to the usual scheme terms and conditions: https://www.hra.nhs.uk/about-us/news-updates/indemnity-cover-nhs-staff-delivering-research/.

17.10 HOME VISITS AND LONE WORKING

We recognise that some participants may face challenges in attending clinic visits due to numerous factors. To address this, visits to participants homes might be offered. Ethical conduct and data integrity will be maintained during these home visits. The safety and well-being of the research staff are paramount. To mitigate potential risks associated with these visits, a detailed risk assessment has been developed. The researchers at recruitment sites, as well as researchers conducting interviews from the central trial team will be trained and equipped to conduct home visits if necessary. Before each visit, the researchers must complete a checklist and a Home Visit Log.

17.11 ARCHIVING

At the end of the trial, all trial data will be stored in line with the 2018 Data Protection Act and archived according to the local SOP. Recruiting sites will be responsible for archiving the source data and Investigator Site Files.

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APPENDICES

APPENDIX 1 - – INFORMATION WITH REGARDS TO SAFETY REPORTING IN NON-CTIMP RESEARCH

	Who	When	How	To Whom
SAE	Chief Investigator	Report to Sponsor within 24 hours of learning of the event Report to the MREC within 15 days of learning of the event	SAE Report form for Non-CTIMPs, available from NRES website.	Sponsor and MREC
Urgent Safety Measures	Chief Investigator	Contact the Sponsor Immediately MREC to be notified Within 3 days	By phone/email Initial notification must set out the reasons for the urgent safety measures and the plan for further action. Where required, Substantial amendment should be submitted as soon as it is possible to do so.	Main REC and Sponsor MREC will aim to give a formal opinion on the substantial amendment within 28 calendar days but will give an opinion in no more than 35 days.
Minor Protocol deviations or GCP non-compliance	Chief Investigator	Contact the Sponsor as soon as possible after learning of the event	By email using the file note template, protocol deviation log and/or file note log templates	Sponsor Voluntary notification to REC manager and to breaches@hra.nhs.uk for information
Serious Breaches	Chief Investigator	Contact the Sponsor immediately MREC to be notified within 7 days of Sponsor notification	By email including details of when the breach occurred, the location, who was involved, the outcome and any information given to participants. An explanation should be given, and the REC informed what further action the sponsor plans to take.	Main REC and Sponsor Reports provided may be referred to the Health Research Authority breaches@hra.nhs.uk for consideration by the Main REC
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC

Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to be sent to the sponsor
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to participants	Main REC with a copy to be sent to the sponsor