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# Psychoeducational and Rehabilitative Intervention to manage Cancer Cachexia (PRICC) for patients and their caregivers: a nonpharmacological prospective mixed methods study protocol

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## ABSTRACT

**Introduction**

Half of all cancer patients experience cachexia, with the prevalence rising above 80% in the last weeks of life. Cancer cachexia (CC) is a complex relational experience that involves the patient-family dyad. There are no studies on the association between the psychoeducational component and the rehabilitative component of dyads for supporting more functional relationships in the management of CC.

The primary objective of this study is to evaluate the feasibility of a psychoeducational intervention combined with a rehabilitative intervention on dyads.

The secondary objective is to improve the quality of life (QoL) and acceptability of the intervention by the dyads.

**Methods and analysis**

This nonpharmacological interventional prospective, mixed methods study includes 30 consecutive cancer patients with cachexia and irreversible cachexia, and their caregivers, assisted by the Specialized Palliative Care Team. The intervention involved 2 components: 1) psychoeducational intervention: 3 weekly face-to-face consultations between dyads and trained nurses to help the dyads cope with involuntary weight loss and strengthening dyadic coping resources; 2) rehabilitation intervention: 3 biweekly educational sessions between dyads and trained physiotherapists focused on self-management, goal-setting and physical activity, and 3 home exercise sessions per week.

The primary endpoint will be adherence to the intervention, indicated by a level of compliance ≥ 50% for both components. The secondary endpoints will be QoL (measured by the Functional Assessment of Anorexia-Cachexia Therapy), caregiver burden (Zarit Burden Scale), physical performance (Hand-Grip strength test and 30-second sit-to stand test), and the acceptability of the intervention (ad hoc semistructured interviews with the dyads and the healthcare professionals).

**Ethics and dissemination**

The study was approved by the Ethics Committee Area Vasta Emilia Nord, Azienda USL - IRCSS Reggio Emilia, Italy, with the number: 73/2019/SPER/IRCCSRE.

**Trial registration**: Retrospectively registe ClinicalTrials.gov: NCT04153019

**Keywords:** cancer cachexia, psychoeducational intervention, rehabilitation, dyad, palliative care

## STRENGHTS AND LIMITATIONS OF THIS STUDY

1. We tested integrated multimodal approach for cancer cachexia: psychoeducational and rehabilitation interventions
2. These two components have strong rational objectives and common modalities, supporting the dyad patient-family
3. The trial will include an integrated qualitative data analysis to provide essential information on feasibility and acceptability
4. The study will be conducted on a number of 30 cancer patients
5. All patients will be assisted by a hospital palliative care unit

## INTRODUCTION

Approximately half of all cancer patients experience cachexia, with the prevalence rising above 80% in the last weeks of life [1-3]. Cancer cachexia (CC) is a continuum with three stages of clinical

relevance: pre-cachexia, cachexia, and refractory cachexia [3-5]. Given the multifaceted pathophysiology and heterogeneous presentation of CC, a personalized treatment approach is necessary to ensure the best possible adherence to the therapeutic proposal [6], especially among patients in palliative care, where a 20% dropout index has been detected [7].

Core component interventions would therefore include nutritional support, as well as exercise-based, anti-inflammatory and educational interventions [3-5]. However, evidence-based practice indicates that it is difficult for patients to comply with all the above mentioned components, with the intake of supplements and non-steroid anti-inflammatory drugs being the most abandoned components [8, 9].

Exercise can reduce the effects of CC by modulating muscle metabolism, reducing insulin resistance and decreasing the inflammatory cascade [10, 11]. Physical activity seems to act as an important anabolic stimulus, especially for patients on chemotherapy, but little is known about its efficacy in the advanced stages of disease [3-5].

The most recent Cochrane review on this subject examined the safety, acceptability and efficacy of exercise in adult patients with cachexia, but no randomized control trial (RCT) has studied physical activity programmes in patients with advanced disease [12].

Cheville et al. [13] conducted an RCT and investigated the feasibility and impact of a programme of physical activity on the physical well-being of cancer patients with life expectancy >6 months who were undergoing radiotherapy. He found that patients in the intervention group experienced subjective improvements in physical performance, but the physical exercise programme did not change their functional status when measured with objective scales.

Oldervoll et al. [14] conducted an RCT to investigate changes in fatigue and physical performance after 8 weeks of physical exercise in cancer patients with a prognosis of less than 2 years. He did not report any differences with respect to the main outcome, but the intervention group showed a statistically significant improvement in muscle strength, as measured by the grip strength test, and an improvement in physical performance, as measured with the shuttle walk test.

Solheim conducted a randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer, offering nutritional counselling and support, anti-inflammatory drugs and exercise programs (aerobic and resistance) to patients in the intervention group vs standard care. The intervention was feasible and safe, but recruitment and compliance were suboptimal [9]. A phase III study is now underway to fully assess the effect of the intervention.

Considering the characteristics of patients with cachexia-anorexia, an exercise programme must be tailored, feasible even at home, and include resistance exercises as a key-component. Some studies have highlighted that resistance exercises stimulate the building of muscle mass and increase strength, thereby reducing the inflammatory response [6-10]. The authors who have studied this topic propose an intervention with a duration between 5 and 8 weeks [9, 13] and a moderate exercise intensity. Other important components of the physical activity programme aimed at motivating the patient and supporting compliance are goal-setting [9, 13] and stretching and relaxation exercises [15].

Cachexia-anorexia syndrome also has effects on psychosocial aspects.

Many qualitative studies have shown that CC is associated with psychosocial distress both for patients and their families, with severe consequences on the quality of life (QoL) and on bereavement depression [16-21]. The psychosocial effects of CC are defined as negative emotions associated with a reduced dietary intake, an involuntary weight loss and the social consequences of these symptoms [16, 17].

Weight loss generates visible physical changes, creating emotional distress [16, 17]. The patients often do not feel comfortable meeting people because their body image is unfamiliar to them, resulting in an alienation from one's self [15, 16].

The involuntary and rapid loss of weight is the cause of concern because it is associated with the fear of imminent death [20, 21]. Consequently, some patients strive to eat more, despite the sense of satiety, expressing unrealistic demands of meals to families. More often, the patients have insight into their clinical condition, and they are more aware of short-term prognosis than their families [20, 21].

The families undertake a series of practices with the aim of satisfying the nutritional needs of patients, including cooking different foods and spending time buying new foods that can stimulate the appetite of their loved ones [19]. Many patients feel uncomfortable in refusing food prepared with great care by family members; consequently, they eat more and more; alternatively, they choose to close themselves off and socially retreat to avoid further discussion [20]. Patients who live with their partners report more eating-related distress than patients who live alone [22].

Studies on psychoeducational approaches to support patients and their families are becoming more common [23-25].

To our knowledge, there are three studies that provide evidence about the important role of psychosocial interventions in the management of CC [23-25].

In particular, a mixed methods qualitative research study [25] developed a complex family-centred psychosocial intervention to help patients with incurable cancer and their family caregivers cope with involuntary weight loss and worsening appetite. This intervention was delivered during face-to-face consultations between 16 patient-family caregiver dyads and a trained nurse. Although 15 dyads reported benefits, the shortcomings should be considered, such as the small sample, the single-centre nature of the intervention and its delivery by a single nurse researcher.

To date, there are no studies on the association between the psychoeducational component and rehabilitative component of dyads to support more functional relationships for the management of CC. The psychoeducational and rehabilitative components have strong rationale, common objectives and modalities compared with the multimodal approaches explored in the literature.

We propose a pilot study that assesses the feasibility and acceptability of a psychoeducational intervention combined with rehabilitation among a population of cancer patients with cachexia and irreversible cachexia undergoing care by the Specialized Palliative Care Team (SPCT).

## METHODS AND ANALYSIS

### Aims

*Primary objective*

To evaluate the feasibility of a psychoeducational intervention combined with a rehabilitative intervention among dyads to treat CC.

*Secondary objective*

To evaluate the QoL (measured by the Functional Assessment of Anorexia-Cachexia Therapy), caregiver burden (measured by Zarit Burden Scale), upper limb physical performance (measured by Hand-Grip strength test), lower limb physical performance (measured by 30-second sit-to stand test) and acceptability of the intervention among dyads (measured by ad hoc semistructured interviews with the dyads and the healthcare professionals).

**Sample and setting**

This nonpharmacological interventional prospective, mixed methods study include 30 consecutive cancer patients with cachexia and irreversible cachexia, as well as their caregivers. All patients will be assisted by the SPCT.

The inclusion criteria were as follows: age>18 years; good command of the Italian language; written informed consent; histologically confirmed tumour diagnosis; presence of irreversible cachexia and cachexia (ESPEN3-5 guidelines, MUST calculation); patients who have identified a caregiver; patients and family members informed of the diagnosis and the objectives of the therapies and who have reported awareness of the disease phase (evaluated by the palliative care physician).

The exclusion criteria were as follows: patients with prognosis <3 months; presence of important mental disorder or dementia; severe sensory deficit; presence of diffuse bone metastases that put the patient at risk of fracture during exercise.

**Intervention**

The intervention includes two components: psychoeducational activities and rehabilitation sessions. The study does not include any restriction of concomitant care or intervention for patients involved.

The nurses and the physiotherapists involved in the intervention will receive pre-enrolment training and supervision during the study.

*Training for nurses and physiotherapists*

The training will include two 4-hour sessions per week for two weeks. The main theories on family types will be reviewed with particular focus on the context of palliative care and the management of the patient/caregiver dyad [26-28]. The contents of the training will focus on the characteristics and methods of conducting a psychoeducational intervention, specifically related to CC. The theoretical part will be integrated into the practical part through the analysis of clinical cases proposed by nurses and physiotherapists, including the analysis of the functioning of the dyads related to food management. This training will be conducted by the PI (L.B.), who is a psychologist, psychotherapist and expert in both palliative care and the support of a functional family system.

*Psychoeducational intervention*

The intervention occurs during a face-to-face consultation between a dyad and two trained nurses. It is designed to help the dyad cope with involuntary weight loss and declining appetite by seeking to strengthen individual and dyadic coping resources. The intervention includes 3 weekly meetings for outpatients (SPCT) to help the dyads talk about weight and eating-related problems and solutions and to address the following topics consecutively:

1. The 'Mapping changing eating habits tool' helps the dyads to talk about their own experience of the patient's change in weight and eating habits (for example, role of the family during the preparation of meals, meanings associated with food, reactions of the patient). The nurse should empower the dyad to understand the nature, course and biological mechanisms of cachexia and acknowledge its negative effects (for example, patients' weight loss, reduced appetite and early satiety). At the end of the meeting, the nurse will collect the main needs reported by the dyad with respect to both the management of mealtimes and the experiences associated with them and will ask the dyads to observe their own relational dynamics with respect to the role that food takes during the day. To conduct this meeting and collect the data,

the nurse uses a tool for evaluating family functioning to construct a first map of the interaction of the dyad [29].

2. The sharing of data collected during the first meeting will occur among both the nurse and the dyad. The nurse will propose practical examples of different ways of managing food in the care of the patients and proposing other ways to support them. In particular, the nurse will facilitate talking about the other person's perspectives, feelings and food and provide for suggestions for how the patient and family can help each other manage weight- and eating-related problems. These reflections are embedded in a naturalistic conversation.
3. A final re-evaluation meeting will focus on the needs that emerged.

*Rehabilitative intervention*

The intervention is conducted by two trained physiotherapists in a face-to-face session with the dyad and includes the following:

1. Three individual outpatient sessions (times T0, T1 and T2; Table 1 shows the time sheet of the intervention) will focus on explaining self-management principles and goal setting and will suggest a tailored physical activity programme to manage or cope with cachexia-related fatigue. The main kind of exercise proposed is strengthening exercises; the choice of exercise and the number of repetitions will be based on the patient's clinical condition, physical performance and preferences. During each session, the dyad is trained by the physiotherapist to perform the new tailored physical activity programme at home, including the use of weights and/or elastic bands with different strengths, if indicated, as well as the use of stretching and relaxation exercises, if needed.
2. Three home sessions of exercises per week will be carried out by the patient on his or her own or with the help of the caregiver for a total of at least 24 sessions over 8 weeks. The patients keep an activity diary, as explained by the physiotherapist, in which they report the actual programme done at home (days, type of exercise, duration, repetitions, problems occurred). The caregiver may help patients perform exercises or keep the diary. The dyad is given a

booklet in which the key concepts from the face-to-face sessions are summarized. There is a personal list of exercises determined in collaboration with physiotherapist (for each exercise, there is the figure and explanation) and a Physical Activity diary that they can keep during home sessions.

**Table 1. The time sheet of the intervention.**

| Assessment | T0 (before intervention) | T1 (2 weeks after T0) | T2 (4 weeks after T0) | T3 (8 weeks after T0) |
|---|---|---|---|---|
| Functional Assessment of Anorexia/Cachexia Therapy (FAACT; patient) | x | | | x |
| Zarit Burden Interview (ZBI; caregiver) | x | | | x |
| Family Function Index (FFI; patient and caregiver) | x | | | |
| Hand-Grip (patient) | x | x | x | x |
| Sit-to-Stand (30CST; patient) | x | x | x | x |
| N sessions for rehabilitative intervention | | x | x | x |
| N sessions for psychoeducational intervention | | | x | |
| Hoc semistructured interviews (dyads) | | | | x |
| Hoc semistructured interviews (healthcare professionals) | | | | x |

*Supervision of the entire process*

At the end of each meeting between the nurse/physiotherapist and dyads, the care team meets with a psychologist/psychotherapist/expert in palliative care and in the family function family system (L.B.) to discuss the data about the dyads' functioning related to CC. The aim is to modulate the next intervention by considering the needs that emerged among the dyads.

In particular, the multimodal intervention is in continuity with the SPCT, which can be activated according to the needs that emerged (palliative care physician, psychologist, nutritionist). The palliative care physician will be informed of any information needs about the prognosis or any clinical condition that may emerge during the psychoeducational intervention. If a psychotherapeutic need emerges, especially among patients with irreversible cachexia, the psychologists of the Psycho-Oncology Unit with skills in palliative care will be activated. Team meetings that take place twice a week may be an additional space for sharing and discussing the global management of patients.

**Data collection strategies**

Recruitment will last 1 year, and all patients assisted by the SPCT will be evaluated during this period. In particular the palliative care physician (ST) proposes to each dyad to participate in the study, and if so they are screened for elegibility by an external researcher (GM) who collect also written informed consent for dyads included. Each patient will be offered both interventions (psychoeducational and rehabilitative) and will not be given the possibility to choose just one.

All replies and reasons for any refusal to participate will be recorded. For each participant, the following basic information will be collected immediately after giving informed consent: age, sex, marital status, family unit, education, profession, religious practice, location of the primary tumour, date of diagnosis, and Karnofsky Performance Status (KPS). Data are collected electronically from the Azienda USL - IRCCS Reggio Emilia database in anonymously and aggregated modalities.

**Analysis**

Two external researchers will be involved in the data analysis.

*Primary objective*

Compliance will be measured as the number of dyads who completed the intervention/the number of involved dyads. Compliance will be assessed for each individual component

(psychosocial/rehabilitative intervention). The overall intervention will be evaluated to be feasible if there is compliance ≥50% for both components.

*Secondary objectives*

The effects of the intervention will be evaluated using the following measures:

- QoL and anorexia-cachexia syndrome related distress will be measured by the Functional Assessment of Anorexia-Cachexia Therapy [30, 31]
- Caregiver burden will be measured by the Zarit Burden Scale [32, 33]
- Upper limb physical performance will be measured by the Hand-Grip strength test [34]
- Lower limb physical performance will be measured by the 30-second sit-to stand test [35]
- Qualitative secondary aims include the exploration of the acceptability, perceived benefits and concerns, strengths and weaknesses of the intervention from the point of view of interviewed dyads and health care professionals.

**Measurement scale**

- *Functional Assessment of Anorexia-Cachexia Therapy (FAACT)* [30, 31].

This scale evaluates anorexia-cachexia-related distress. It derives from the Functional Assessment of Cancer Therapy-General (FACT-G) and includes four subscales developed and validated to measure health-related quality of life, particularly in cancer patients undergoing therapy: physical well-being, social/family well-being, emotional well-being and functional well-being. In addition to the 28 items across these 4 subscales, 12 specific items were added to assess problems related to the presence of anorexia-cachexia. Response options for reach item ranged from 0 ‘Not at all’ to 4 ‘Very much’; higher scores indicate a greater quality of life. The questionnaire can be self-reported or administered by a trained person.

In our study, we will use only the sub-scale related to anorexia-cachexia self-reported by the patient [26].

- *Zarit burden scale* [32, 33].

The Zarit Burden Interview (ZBI) is a 22-item instrument for measuring the caregiver's perceived burden of providing family care. The 22 items are assessed on a 5-point Likert scale, ranging from 0 = 'never' to 4 = 'nearly always'. Item scores are added to obtain a total score ranging from 0 to 88, with higher scores indicating greater burden. The questions focus on major areas such as caregiver's health, psychological well-being, finances, social life and the relationship between the caregiver and the patient.

This scale has been widely used for many years, has been translated into 18 languages [28], and has been validated in Italian [29].

In this study, it will be self-reported by the caregiver.

- *Family Relationship Index* [29].

The self-reported Family Relationship Index is composed of 12 items with true/false answers and it is specifically used to evaluate family functioning in the palliative care setting. It is used as a screening tool to preventively assess families at risk of developing psychological distress associated with diseases with poor prognoses. Family members report their perceived level of cohesion, expression and resolution of conflicts. The scale identifies 5 family types that are distributed along a continuum ranging from families with good adaptation to the disease (supportive and able to face and resolve conflicts) to dysfunctional families with poor adaptation (hostile and silent, where a high index of anger is detected or latent). There is a defined intermediate family type that is placed between these types of family functioning (with good adaptation and poor adaptation).

In our study, the scale will be used to collect data useful for the evaluation of family functioning, associating them specifically with cachexia and the role of food in assistance (Do we talk about it in the family? Do we tend to avoid the subject? Is it possible to talk about the emotional problems related to cachexia? Is the problem faced or avoided?). The scale will be self-completed separately by the patient and the caregiver.

The data collected will be used by nurses during the psychoeducational intervention as support in the evaluation of the dyad interaction modalities.

There is a validated Italian version [28].

- *Hand-Grip strength test* [34].

This test is administered using a dynamometer to quantitatively and objectively measure the isometric muscle strength of the patient's upper limbs. The assessor must calculate the average of 3 consecutive tests. This test has been validated for healthy adults, elderly and stroke patients. It has been used as a measure of physical performance in some studies with patients with cancer, even in advanced stages.

- *30-second sit-to stand test* [35].

This test evaluates the lower limb strength in the sit-to stand function.

The assessor asks the patient to get up from a chair without the support of the arms. The number of repetitions the patient can do in 30 seconds is the score of the test.

This test has been validated for patients with osteoarthritic and elderly problems. It has been used as a measure of physical performance in some studies with cancer patients, even in advanced stages.

- Ad hoc semistructured interviews of the dyad will be conducted one month after the intervention. The interviews will be conducted by a research medical doctor (G.M.) trained in qualitative research and focus groups and by the PI of the study (L.B.) for a total of 7 interviews. The dyads will be chosen based on pre and post-intervention results, with particular attention given to identifying the participants who have reported good adherence to the intervention and participants who have reported difficulties.

- Ad hoc semistructured interviews of nurses and physiotherapists who participated in the study will also be conducted. The interviews will be conducted by the research nurse (G.A.) and by a research medical doctor (G.M.) for a total of 4 interviews corresponding to the operators involved (2 nurses and 2 physiotherapists).

**Data analysis**

The data analysis will be conducted by the Clinical and Statistical Studies Unit - IRCCS Reggio Emilia.

Sample size: Since this is a pilot study to collect data on the feasibility of the intervention, a formal calculation is not carried out; 30 patients will be assessed, in accordance with the criteria of opportunity and feasibility. The statistical analysis will be descriptive: the primary endpoint will be represented by descriptive statistics (average, median, minimum, maximum, remarkable percentiles, central tendency index (with 95% CI), standard deviation, and shape indexes).

The secondary endpoint will be the descriptive representation (for T0, T1, T2 and T3) of the endpoints and of the variations detected between T0 and T3.

*The qualitative analysis*

The qualitative analysis will be performed as described below. Recordings of the interviews will be transcribed verbatim and then analysed using thematic analysis to explore the content and context of responses [36, 37].

Each transcript will be independently labelled by two researchers, who will resolve differences in labelling. Throughout an iterative process, they will inductively identify a few subthemes. Finally, a third researcher will revise both the transcripts and the preliminary thematic analysis and regroup and rename some themes and subthemes with the objective of describing them by highlighting commonalities and differences between the perspectives of the three 'actors' involved. This revision will be discussed and amended with the other researchers involved in the qualitative analysis.

## ETHICS AND DISSEMINATION

The study was approved by the Ethics Committee Area Vasta Emilia Nord, Azienda USL - IRCSS Reggio Emilia, Italy, with the number 73/2019/SPER/IRCCSRE.

All study participants will be informed in detail by the investigator of the aims and objectives of the study and must sign informed consent for the study and processing of personal data that will be filed together with the study documentation. Consent to participate in the study was requested and collected by the proposing doctor or by the researcher in charge of the T0 assessment. Each participant has the right to withdraw their membership in the study at any time.

All data collected are restricted by Ethics Committee of the Vast Northern Emilia (Italy) in order to protect participant privacy. The data will be available from the corresponding author (LB), upon reasonable request, with the permission of Azienda USL - IRCCS Reggio Emilia, Italy.

The study will be conducted in accordance with this protocol, any amendments introduced and authorized, and the ethical principles of the Helsinki Declaration.

The authors will be provided the publication of this study protocol and its results through publication in international scientific journals.

**List of abbreviations**

Cancer cachexia: CC

Quality of Life: QoL

Specialized Palliative Care Team: SPCT

Karnofsky Performance Status: KPS

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**Authors' contributions**

L.B. analyzed the literature on cancer cachexia, devised the study, coordinated the working of team. She contributed to the conception of the study, to the draft of the manuscript and to its critical revision for important intellectual content, supporting each member of the team. She conducted the healthcare professionals training and handled the presentation of the protocol to the Ethics Committee. She approves the final version to be submitted and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of it are appropriately investigated and resolved.

E.B. contributed to the design and drafting of the study protocol and the implementation of the psychoeducational intervention. She also collaborated in the writing and rereading of the manuscript.

C.A. contributed to the design and drafting of the study protocol and the implementation of the psychoeducational intervention. She also collaborated in the writing and rereading of the manuscript.

M.A.A. contributed to the design and drafting of the study protocol and the implementation of the rehabilitation intervention. She also collaborated in the writing and rereading of the manuscript.

M.D. contributed to the design of the study protocol and the implementation of the rehabilitation intervention. She also collaborated in the drafting and rereading of the manuscript.

S.F. contributed to the research project development, to the rehabilitation protocol and to the draft of the manuscript.

G.F.M. gave a methodological contribution, in particular on qualitative methods.

S.C. contributed to the conception of the study, to the draft of the manuscript and to its critical revision for important intellectual content.

S.T. analyzed the literature on cancer cachexia. She contributed to the conception of the study, to the draft of the manuscript and to its critical revision for important intellectual content. She coordinates the patient enrollment in the study as a head of the Specialized Palliative Care Team.

All authors read and approved the final manuscript.

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***Competing interests***

The authors declare that they have no competing interests.

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# Comitato Etico dell'Area Vasta Emilia Nord

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Coordinatore S.C. Infrastruttura Ricerca e Statistica
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SEDE

**Oggetto: 73/2019/SPER/IRCCSRE –** Intervento psico-educativo e riabilitativo per paziente con cachessia - "Intervento psico-educativo e riabilitativo per il paziente oncologico con cachessia e il suo caregiver: uno studio di fattibilità"
*Promotore NON COMMERCIALE: A.U.S.L. – IRCCS di Reggio Emilia*
*Sperimentatore: Dott.ssa Loredana Buonaccorso*
*Centro clinico: Unità di Psico-Oncologia – Presidio SMN*

*Elenco della documentazione esaminata*

1_Lettera_di_intenti versione 1 del 29.01.2019 (2)
1_Lettera_di_intenti versione 1 del 29.01.2019 FIRMATA
2_Protocollo Versione 1 del 29.01.2019
3_ Sinossi versione 1 del 29.01.2019
4_Foglio_Informativo paziente Versione 1 del 29.01.2019
4_Foglio_Informativo_caregiver Versione 1 del 29.01.2019 (3)
5_ Modulo_di_Consenso Versione 1 del 29.01.2019
6_ Nota_Informativa_al_Trattamento_Dati_Personali paziente Versione 1 del 29.01.2019
6_Nota_Informativa_al_Trattamento_Dati_Personali caregiver 20Versione 1 del 29.01.2019
7_LETTERA_MMG_versione 1 del 29.01.2019
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9_CV sperimentatore versione 1 del 29.01.2019
10_Modulo_di_fattibilita_locale_Versione 1 del 29.01.2019 FIRMATO
10_Modulo_di_fattibilita_locale_Versione 1 del 29.01.2019
11_Scale di Valutazione versione 1 del 29.01.2019

Il Comitato Etico, nella seduta del 18/03/2019, esprime all'unanimità **PARERE FAVOREVOLE** alla conduzione dello studio.

**Si ricorda che lo studio potrà essere avviato solo dopo aver ricevuto il nulla osta, ai sensi dell'art. 7 della L.R. 9/2017, da parte del Direttore Generale, di cui verrà data notizia, e che l'avvio della sperimentazione clinica e dello studio, in assenza del nullaosta da parte del Direttore Generale, è fonte di responsabilità disciplinare ed è rilevante ai fini della responsabilità civile, amministrativa e contabile dello sperimentatore.**

# Comitato Etico dell'Area Vasta Emilia Nord

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Resta inteso che:

- ai fini del monitoraggio dell'andamento dello studio in oggetto, lo **Sperimentatore Responsabile** dovrà comunicare al Comitato Etico, facendo riferimento alla Segreteria di propria competenza, le seguenti informazioni **relativamente a questo singolo centro sperimentale**: data di inizio arruolamento, data di fine arruolamento e data di conclusione dello studio. In ogni caso, **a partire dall'anno di approvazione dello studio** e fino alla sua conclusione, **almeno una volta all'anno e comunque entro e non oltre il 31 dicembre**, dovrà essere fornito un rapporto annuale sullo stato di avanzamento dello studio. Per le suddette comunicazioni è possibile utilizzare il modulo disponibile sul sito web del Comitato Etico AVEN. Il modulo compilato, firmato e datato, andrà inviato in originale e in formato elettronico.

Si ricorda allo sperimentatore di attivare la procedura di designazione degli autorizzati al trattamento dei dati personali nell'ambito di studi e sperimentazioni cliniche, come da Deliberazione del Direttore Generale n. 284 del 25/07/2018. Il fac-simile del documento potrà essere richiesto alla Segreteria Locale di Reggio Emilia.

**NOTA:** per qualsiasi successiva comunicazione relativa allo studio in oggetto è indispensabile fare riferimento al codice interno CE che identifica lo studio (indicato nell'oggetto) e alla data della seduta di approvazione.

*IL PRESIDENTE*

Firmato digitalmente da:CALANDRA BUONAURA SEBASTIANO
Data:19/03/2019 11:38:14

**Allegato:** Elenco Componenti CE AVEN.

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BMJ Open

# Psychoeducationl and Rehabilitative Intervention to manage Cancer Cachexia (PRICC) for patients and their caregivers: protocol for a single arm feasibility trial

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# Psychoeducationl and Rehabilitative Intervention to manage Cancer Cachexia (PRICC) for patients and their caregivers: protocol for a single arm feasibility trial

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## ABSTRACT

### Introduction

Half of all cancer patients experience cachexia, with the prevalence rising above 80% in the last weeks of life. Cancer cachexia (CC) is a complex relational experience that involves the patient-family dyad. There are no studies on the association between the psychoeducational component and the rehabilitative component of dyads for supporting more functional relationships in the management of CC.

The primary objective of this study is to evaluate the feasibility of a psychoeducational intervention combined with a rehabilitative intervention on dyads.

The secondary objective is to improve the quality of life (QoL) and acceptability of the intervention.

**Methods and analysis**

This mixed methods study with a nonpharmacological interventional prospective includes 30 consecutive cancer patients with cachexia and refractory cachexia and their caregivers, assisted by the Specialized Palliative Care Team. The recruitment will last one year. The intervention involves 2 components: 1) Psychoeducational intervention: 3 weekly face-to-face consultations between dyads and trained nurses to help the dyads cope with involuntary weight loss and strengthening dyadic coping resources; 2) Rehabilitation intervention: 3 biweekly educational sessions between dyads and trained physiotherapists focused on self-management, goal-setting, physical activity with 3 home exercise sessions per week.

The primary endpoint will be in adherence to the intervention, indicated by a level of completion greater than or equal to 50% in both components. The secondary endpoints will be QoL (Functional Assessment of Anorexia-Cachexia Therapy), caregiver burden (Zarit Burden), physical performance (Hand-Grip strength and 30-second sit-to-stand test), and the acceptability of the intervention (ad hoc semi-structured interviews with the dyads and the healthcare professionals).

**Ethics and dissemination**

The study was approved by the Ethics Committee Area Vasta Emilia Nord, Azienda USL-IRCSS Reggio Emilia, Italy, number: 73/2019/SPER/IRCCSRE. The authors will provide the dissemination of the results through publication in international scientific journal.

**Trial registration**: Retrospectively register ClinicalTrials.gov: NCT04153019

**Keywords:** cancer cachexia, psychoeducational intervention, rehabilitation, dyad, palliative care

## STRENGHTS AND LIMITATIONS OF THIS STUDY

1. A small size and no control group, as in most feasibility studies
2. Innovative bimodal approach, combining psychoeducational and rehabilitative intervention in order two manage cancer cachexia
3. Intervention address to dyads (patients-caregiver) suffering from cancer cachexia and not only to patients
4. Collection of both qualitative and quantitative data due condition of patients involved
5. Training and recurrent supervision of nurses and physiotherapists involved in the intervention

## INTRODUCTION

Approximately half of all cancer patients experience cachexia, with the prevalence rising above 80% in the last weeks of life [1-3]. Cancer cachexia (CC) is a continuum with three stages of clinical relevance: pre-cachexia, cachexia, and refractory cachexia [3-5]. Given the multifaceted pathophysiology and heterogeneous presentation of CC, a personalized treatment approach is

necessary to ensure the best possible adherence to the therapeutic proposal [6], especially among patients in palliative care, where a 20% dropout index has been detected [7].

Core component interventions should, therefore, include nutritional support, as well as exercise-based, anti-inflammatory, and educational interventions [3-5]. However, evidence-based practice indicates that it is difficult for patients to comply with all of these components, with the intake of supplements and non-steroid, anti-inflammatory drugs being the most abandoned components [8].

Exercise can reduce the effects of CC by modulating muscle metabolism, reducing insulin resistance, and decreasing the inflammatory cascade [9, 10]. Physical activity seems to act as an important anabolic stimulus, especially for patients on chemotherapy, but little is known about its efficacy in the advanced stages of disease [3-5].

The most recent Cochrane review on this subject examined the safety, acceptability, and efficacy of exercise in adult patients with cachexia, but no randomized control trial (RCT) has studied physical activity programs in patients with advanced diseases [11].

Cheville et al. [12] conducted a RCT and investigated the feasibility and impact of a program of physical activity on the physical well-being of cancer patients with life expectancy of greater than 6 months who were undergoing radiotherapy. He found that patients in the intervention group experienced subjective improvements in physical performance, but the physical exercise program did not change their functional status when measured with an objective scale.

Oldervoll et al. [13] conducted a RCT to investigate changes in fatigue and physical performance after 8 weeks of physical exercise in cancer patients with a prognosis of less than 2 years. He did not report any differences with respect to the main outcome, but the intervention group showed a statistically significant improvement in muscle strength, as measured by the grip strength test, and an improvement in physical performance, as measured with the Shuttle walk test.

Solheim conducted a randomized Phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer, offering nutritional counseling and support, anti-inflammatory drugs, and exercise programs (e.g., aerobic and resistance) to patients in the

intervention group as opposed to standard care. The intervention was feasible and safe, but recruitment and compliance were suboptimal for exercise [14]. A Phase III study is now underway to fully assess the effect of the intervention.

Considering the characteristics of patients with cachexia-anorexia, an exercise program must be tailored and feasible at home and include resistance exercises as a key-component. Some studies have highlighted that resistance exercises stimulate the building of muscle mass and increase strength, thereby reducing the inflammatory response [6-9]. The authors who have studied this topic proposed an intervention with a duration between 5 and 8 weeks [9, 12] and a moderate exercise intensity. Other important components of the physical activity program aimed at motivating the patient and supporting compliance for goal setting [9, 12], stretching, and relaxation exercises [15].

Cachexia-anorexia syndrome also has effects on psychosocial aspects.

Many qualitative studies have shown that CC is associated with psychosocial distress for both patients and their families, with severe consequences on the quality of life (QoL) and on bereavement depression [16-21]. The psychosocial effects of CC are defined as negative emotions associated with a reduced dietary intake, an involuntary weight loss, and social consequences from these symptoms [16, 17].

Weight loss generates visible physical changes, creating emotional distress [16, 17]. The patients often do not feel comfortable meeting people because their body image is unfamiliar to them, resulting in an alienation from one's self [15, 16].

The involuntary and rapid loss of weight is a cause of concern because it is associated with the fear of imminent death [20, 21]. Consequently, some patients strive to eat more, despite the sense of satiety, expressing unrealistic demands of meals to families. The patients often have insight into their clinical condition, and they are more aware of the short-term prognosis than their families [20, 21].

The families undertake a series of practices with the aim of satisfying the nutritional needs of patients, including cooking different foods and spending time buying new foods that can stimulate the appetite of their loved ones [19]. Many patients feel uncomfortable in refusing food prepared with great care

by family members, and consequently, they eat more and more. Alternatively, they choose to close themselves off and socially retreat to avoid further discussion [20]. Patients who live with their partners report more eating-related distress than patients who live alone [22].

Studies on psychoeducational approaches to support patients and their families are becoming more common [23-25].

To our knowledge, there are three studies that provide evidence about the important role of psychosocial interventions in the management of CC [23-25].

In particular, a mixed methods qualitative research study [25] developed a complex family-centered psychosocial intervention to help patients with incurable cancer and their family caregivers to cope with involuntary weight loss and worsening appetite. This intervention was delivered during face-to-face consultations between 16 patient-family caregiver dyads and a trained nurse. Although 15 dyads reported benefits, the shortcomings must be considered, such as the small sample, the single-centered nature of the intervention and its delivery by a lone nurse researcher.

To date, there are no studies on the association between the psychoeducational component and the rehabilitative component of dyads to support more functional relationships for the management of CC. The psychoeducational and rehabilitative components have a strong rationale, common objectives, and modalities compared to the multimodal approaches explored in the literature. We propose a prospective mixed methods pilot study that assesses the feasibility of a psychoeducational intervention combined with rehabilitation among a population of cancer patients with cachexia and refractory cachexia undergoing care by the Specialized Palliative Care Team (SPCT).

## METHODS AND ANALYSIS

### Aims

*Primary objective*

To evaluate the feasibility of psychoeducational intervention combined with the rehabilitative

intervention among dyads to treat CC, assessed through completion rate

*Secondary objective*

- To evaluate the QoL (measured by the Functional Assessment of Anorexia-Cachexia Therapy), caregiver burden (measured by Zarit Burden Scale), upper limb physical performance (measured by Hand-Grip strength test), lower limb physical performance (measured by 30-second sit-to stand test). These evaluations are aimed to collect descriptive data that will be used to establish power calculations required for a full-scale study.
- To evaluate the acceptability of the intervention among dyads (measured by ad hoc semi-structured interviews with the dyads and the healthcare professionals).

**Sample and setting**

This study includes a convenient sample of 30 consecutive cancer patients with cachexia and refractory cachexia, as well as their caregivers. The study will be conducted in Palliative Care Unit, in collaboration with Physical Medicine and Rehabilitation Unit, of Santa Maria Nuova Hospital, Azienda USL-IRCSS of Reggio Emilia. All patients will be assisted by the SPCT, and the recruitment will last one year.

The inclusion criteria are as follows: age greater than 18 years; good command of the Italian language; written consent; histologically confirmed tumor diagnosis; presence of cachexia and refractory cachexia (5, MUST calculation); an identified caregiver by the patient; patients and family members informed of the diagnosis; and the objectives of the therapies who have reported awareness of the disease phase (evaluated by the palliative care physician).

The exclusion criteria are as follows: patients with prognosis of less than 3 months; presence of important mental disorder or dementia; severe sensory deficit; presence of diffused bone metastases that put the patient at risk of fracture during exercise.

**Intervention**

The intervention includes two components: psychoeducational activities and rehabilitation sessions. The study does not include any restriction of concomitant care or intervention for patients involved. The two nurses and the two physiotherapists involved in the intervention will receive pre-enrollment training and supervision during the study.

*Training for nurses and physiotherapists*

The training will include two 4-hour sessions per week for two weeks. The main theories on family types will be reviewed with a particular focus on the context of palliative care and the management of the patient/caregiver dyad [26-28]. The contents of the training will focus on the characteristics and methods of conducting a psychoeducational intervention, specifically related to CC. The theoretical component will be integrated into the practical part through the analysis of clinical cases proposed by nurses and physiotherapists, including the analysis of the functioning of the dyads related to food management. This training will be conducted by the PI (L.B.), who is a psychologist, psychotherapist, and expert in both palliative care and the support of a functional family system.

*Psychoeducational intervention*

The intervention occurs during a face-to-face consultation between a dyad and trained nurses (Table 1 shows the timeline of assessment; Figure 1 shows the timeline of the intervention). It is designed to help the dyad cope with involuntary weight loss and declining appetite by seeking to strengthen individual and dyadic coping abilities. The intervention includes 3 meeting, one a week, for outpatients (SPCT) to help the dyads discuss weight and eating-related problems and solutions and to address the following topics consecutively:

1. The "Mapping changing eating habits tool" helps the dyads to talk about their own experience of the patient's weight change and eating habits (e.g., the role of the family during the preparation of meals, meanings associated with food, and reactions of the patient). The nurse should empower the dyad to understand the nature, course, and biological mechanisms of cachexia and acknowledge its negative effects (e.g., patients' weight loss, reduced appetite and early satiety). At the end of the meeting, the nurse will record the main needs reported by

the dyad with respect to both the management of mealtimes and the experiences associated with them and will ask the dyads to observe their own relational dynamics of the role that food takes during the day. To conduct this meeting and collect data, the nurse will use a tool for evaluating family functioning to construct a first map of the interaction of the dyad [29].

2. The sharing of data collected during the first meeting will occur amongst both the nurse and the dyad. The nurse will propose practical examples of different ways of managing food in the care of the patients and propose other ways to support them. In particular, the nurse will facilitate discussion about the other person's perspectives, feelings, and food and provide suggestions for how the patient and family can help each other manage weight- and eating-related problems. These reflections are embedded in a naturalistic conversation.
3. A final re-evaluation meeting will focus on the needs that will have emerged.

*Rehabilitative intervention*

The intervention is conducted by a trained physiotherapist in a face-to-face session with the dyad and includes the following:

1. Three individual outpatient sessions (times T0, T1 and T2; Table 1 shows the timeline of assessment; Figure 1 shows the timeline of the intervention) will focus on explaining self-management principles and setting goals. The physiotherapist will suggest a tailored physical activity program to manage or cope with cachexia-related fatigue. The main type of exercise to be proposed is strengthening exercises; the choice of exercise and the number of repetitions will be based on the patient's clinical condition, physical performance, and preferences. During each session, the dyad is trained by the physiotherapist to perform the new tailored physical activity program at home, including the use of weights and/or elastic bands with different strengths, if indicated, as well as the use of stretching and relaxation exercises, if necessary.
2. Three home sessions of exercises per week will be carried out by the patient on his or her own or with the help of the caregiver for a total of minimum 24 sessions over 8 weeks. The patients

will keep an activity diary, as previously explained by the physiotherapist, in which they will report the details of the program done at home (e.g., days, type of exercise, duration, repetitions, problems occurred). The caregiver may help patients perform exercises or record in the diary. The dyad is given a booklet in which the key concepts from the face-to-face sessions will be summarized. There is a personal list of exercises determined in collaboration with physiotherapist (i.e., for each exercise, there is the figure and explanation) and the Physical Activity diary that the patients are asked to keep for the home exercises.

**Table 1. The timeline of assessment**

| Assessment | T0 (before intervention) | T1 (2 weeks after T0) | T2 (4 weeks after T0) | T3 (8 weeks after T0) |
|---|---|---|---|---|
| Functional Assessment of Anorexia/Cachexia Therapy (FAACT; patient) | x | | x | |
| Zarit Burden Interview (ZBI; caregiver) | x | | x | |
| Family Function Index (FFI; patient and caregiver) | x | | x | |
| Hand-Grip (patient) | x | x | x | x |
| Sit-to-Stand (30CST; patient) | x | x | x | x |
| Number of sessions attended for rehabilitative intervention | | x | x | x |
| Number of sessions attended for psychoeducational intervention | | | x | |
| Ad-Hoc semi-structured interviews (dyads) | | | | x |

| Assessment | T0 (before intervention) | T1 (2 weeks after T0) | T2 (4 weeks after T0) | T3 (8 weeks after T0) |
|---|---|---|---|---|
| Ad-Hoc semi-structured interviews (healthcare professionals) | | | | x |

*Supervision of the entire process*

At the end of each meeting between the nurse/physiotherapist and dyads, the care team will meet with a psychologist/psychotherapist/expert in palliative care and in the family function family system (L.B.) to discuss the data concerning the dyads' functioning related to CC. The aim will be to modulate the next intervention by considering the needs that emerged among the dyads.

In particular, the bimodal intervention is in continuity with the SPCT, which can be activated according to the needs that have emerged (e.g., palliative care physician, psychologist, nutritionist). The palliative care physician will be informed of any information needs about the prognosis or any clinical condition that may emerge during the psychoeducational intervention. If a psychotherapeutic need emerges, especially amongst patients with refractory cachexia, the psychologists of the Psycho-Oncology Unit with skills in palliative care will be notified. Team meetings that take place twice a week may provide an additional space for sharing and discussing the global management of patients.

**Data collection strategies**

Recruitment will last for 1 year, and all patients assisted by the SPCT will be evaluated during this period. In particular, the palliative care physician (S.T.) will propose to each dyad meeting inclusion criteria to participate to the study, then an external researcher (G.M.) will collect written informed consent and baseline evaluation. Each patient will be offered both interventions (psychoeducational and rehabilitative) and will not be given the possibility to choose just one.

All replies and reasons for any refusal to participate will be recorded. For each participant, the following basic information will be collected immediately after giving informed consent: age, sex, marital status, family unit, education, profession, religious practice, location of the primary tumor, date of diagnosis, and Karnofsky Performance Status (KPS). Data will be collected electronically from the Azienda USL-IRCCS of Reggio Emilia database in anonymously and aggregated modalities.

**Analysis**

Two external researchers will be involved in the data analysis.

*Primary objective*

Completion will be measured as the number of dyads who completed the intervention/the number of involved dyads. Completion will be assessed for each individual component (psychosocial/rehabilitative intervention). The overall intervention will be identified as feasible if there is completion ≥50% for both components.

*Secondary objectives*

The effects of the intervention are collected to have descriptive data that will be used to establish power calculations required for a full-scale study.

The effects of the intervention will be evaluated using the following measures:

- QoL and anorexia-cachexia syndrome related distress will be measured by the Functional Assessment of Anorexia-Cachexia Therapy [30, 31]
- Caregiver burden will be measured by the Zarit Burden Scale [32, 33]
- Upper limb physical performance will be measured by the Hand-Grip strength test [34]
- Lower limb physical performance will be measured by the 30-second sit-to stand test [35]
- Qualitative secondary aims include the exploration of the acceptability, perceived benefits and concerns, strengths and weaknesses of the intervention from the point of view of interviewed dyads and healthcare professionals.

**Measurement scale**

- *Functional Assessment of Anorexia-Cachexia Therapy (FAACT)* [30, 31].

This scale evaluates anorexia-cachexia-related distress. It derives from the Functional Assessment of Cancer Therapy-General (FACT-G) and includes four subscales developed and validated to measure health-related quality of life, particularly in cancer patients undergoing therapy: physical well-being, social/family well-being, emotional well-being, and functional well-being. In addition to the twenty-eight items across these four subscales, twelve specific items were added to assess problems related to the presence of anorexia-cachexia. Response options for reach item ranged from 0 as 'Not at all' to 4 as 'Very much' with higher scores indicating a greater quality of life. The questionnaire can be self-reported or administered by a trained person.

In our study, we will use only the sub-scale related to anorexia-cachexia self-reported by the patient [26].

- *Zarit burden scale* [32, 33].

The Zarit Burden Interview (ZBI) is a 22-item instrument for measuring the caregiver's perceived burden of providing family care. The 22 items are assessed on a 5-point Likert scale, ranging from 0 = 'never' to 4 = 'nearly always'. Item scores are added to obtain a total score ranging from 0 to 88, with higher scores indicating greater burden. The questions focus on major areas such as caregiver's health, psychological well-being, finances, social life and the relationship between the caregiver and the patient.

This scale has been widely used for many years and has been translated into 18 languages [28] and validated in Italian [29].

In this study, it will be self-reported by the caregiver.

- *Family Relationship Index* [29].

The self-reported Family Relationship Index is composed of 12 items with true/false answers, and it is specifically used to evaluate family functioning in the palliative care setting. It is used as a

screening tool to preventively assess families at risk of developing psychological distress associated with diseases with poor prognoses. Family members report their perceived level of cohesion, expression, and resolution of conflicts. The scale identifies 5 family types that are distributed along a continuum ranging from families with good adaptation to the disease (i.e., supportive and able to face and resolve conflicts) to dysfunctional families with poor adaptation (i.e., hostile and silent, where a high index of anger is detected or latent). There is a defined intermediate family type that is placed between these types of family functioning (e.g., with good adaptation and poor adaptation).

In our study, the scale will be used to collect data useful for the evaluation of family functioning, associating them specifically with cachexia and the role of food in assistance (i.e., Do we talk about it in the family? Do we tend to avoid the subject? Is it possible to talk about the emotional problems related to cachexia? Is the problem faced or avoided?). The scale will be self-completed separately by the patient and the caregiver.

The data collected will be used by nurses during the psychoeducational intervention as support in the evaluation of the dyad interaction modalities.

There is a validated Italian version [28].

- *Hand-Grip strength test* [34].

This test is administered using a dynamometer to quantitatively and objectively measure the isometric muscle strength of the patient's upper limbs. The assessor must calculate the average of 3 consecutive tests. This test has also been validated for healthy adults, elderly and stroke patients. It has been used as a measure of physical performance in some studies with patients with cancer, even in advanced stages.

- *30-second sit-to stand test* [35].

This test evaluates the lower limb strength in the sit-to-stand function.

The assessor asks the patient to get up from a chair without the support of the arms. The number of repetitions the patient can do in 30 seconds is the score of the test.

This test has been validated for patients with osteoarthritic and elderly problems. It has been used as a measure of physical performance in some studies with cancer patients, even in advanced stages.

- Ad hoc semi-structured interviews of the dyad will be conducted one month after the intervention. The interviews will be conducted by a research medical doctor (G.M.) trained in qualitative research and focus groups and by the PI of the study (L.B.) for a total of 7 interviews. The dyads will be chosen based on pre- and post-intervention results, with a particular attention to identifying the participants who have reported good adherence to the intervention and participants who have reported difficulties.

- Ad hoc semi-structured interviews of nurses and physiotherapists who participated in the study will also be conducted. The interviews will be conducted by the research nurse (G.A.) and by a research medical doctor (G.M.) for a total of 4 interviews corresponding to the operators involved (2 nurses and 2 physiotherapists).

**Data analysis**

The data analysis will be conducted by the Clinical and Statistical Studies Unit Azienda USL-IRCCS of Reggio Emilia.

Sample size: Since this is a pilot study to collect data on the feasibility of the intervention, a formal calculation is not carried out. Thirty patients will be assessed, in accordance with the criteria of opportunity and feasibility. The statistical analysis will be descriptive; the primary endpoint will be represented by descriptive statistics (average, median, minimum, maximum, remarkable percentiles, central tendency index (with 95% CI), standard deviation, and shape indexes).

The secondary endpoint will be the descriptive representation (for T0, T1, T2 and T3) of the endpoints and of the variations detected between T0 and T3.

*The qualitative analysis*

The qualitative analysis will be performed as described below. Recordings of the interviews will be transcribed verbatim and then analysed using thematic analysis to explore the content and context of responses [36, 37].

Each transcript will be independently labelled by two researchers, who will resolve differences in labelling. Throughout an iterative process, they will inductively identify a few subthemes. Finally, a third researcher will revise both the transcripts and the preliminary thematic analysis, regroup, and rename some themes and subthemes with the objective of describing them by highlighting commonalities and differences between the perspectives of the three 'actors' involved. This revision will be discussed and amended with the other researchers involved in the qualitative analysis.

**Patient and Public Involvement**

No patients or association were involved in the design or conduction of the study.

However, the development of PRICC intervention was informed by literature research and patients' priorities collected by the SPCT during the clinical practice.

## ETHICS AND DISSEMINATION

The study was approved by the Ethics Committee Area Vasta Emilia Nord, Azienda USL - IRCSS of Reggio Emilia, Italy, with the number 73/2019/SPER/IRCCSRE.

All study participants will be informed in detail of the aims and objectives of the study by the investigator and must sign a consent form for the study and processing of personal data that will be filed together with the study documentation. Consent to participate in the study will be requested and collected by the proposing doctor or by the researcher in charge of the T0 assessment. Each participant has the right to withdraw their membership in the study at any time.

All data collected are restricted by Ethics Committee of the Vast Northern Emilia (Italy) in order to protect participant privacy. The data will be available from the corresponding author (L.B.), upon reasonable request, with the permission of Azienda USL-IRCCS of Reggio Emilia, Italy.

The study will be conducted in accordance with this protocol along with any amendments introduced and authorized, as well as the ethical principles of the Helsinki Declaration.

The authors will provide the dissemination of the study results through publication in international scientific journals.

**List of abbreviations**

Cancer cachexia: CC

Quality of Life: QoL

Specialized Palliative Care Team: SPCT

Karnofsky Performance Status: KPS

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**Authors' contributions**

L.B. analyzed the literature on cancer cachexia, devised the study, coordinated the working of team. She contributed to the conception of the study, to the draft of the manuscript and to its critical revision for important intellectual content, supporting each member of the team. She conducted the healthcare professionals training and handled the presentation of the protocol to the Ethics Committee. She approves the final version to be submitted and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of it are appropriately investigated and resolved.

E.B. contributed to the design and drafting of the study protocol and the implementation of the psychoeducational intervention. She also collaborated in the writing and rereading of the manuscript.

C.A. contributed to the design and drafting of the study protocol and the implementation of the psychoeducational intervention. She also collaborated in the writing and rereading of the manuscript.

M.A.A. contributed to the design and drafting of the study protocol after the analysis of the literature on cachexia related fatigue. She also contributed to the implementation of the rehabilitation intervention and she collaborated in the writing and rereading of the manuscript.

M.D. contributed to the design of the study protocol after the analysis of the literature on cachexia related fatigue. She also contributed to the implementation of the rehabilitation intervention. She also collaborated in the drafting and rereading of the manuscript.

S.F. contributed to the research project development and to the rehabilitation protocol, after the analysis of the literature on cachexia related fatigue. She also collaborated in the drafting and rereading of the manuscript.

G.M. gave a methodological contribution, in particular on qualitative methods.

S.C. contributed to the conception of the study, to the draft of the manuscript and to its critical revision for important intellectual content.

S.T. analyzed the literature on cancer cachexia. She contributed to the conception of the study, to the draft of the manuscript and to its critical revision for important intellectual content. She coordinates the patient enrollment in the study as a head of the Specialized Palliative Care Team.

All authors read and approved the final manuscript.

***Competing interests***

The authors declare that they have no competing interests.

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Funders had no role in the definition of the study design, in the collection, analysis or interpretation of data, in the writing of the report or in the decision to submit the article for publication.

**Figure 1.** Timeline of the intervention

**Word Count:** 3927

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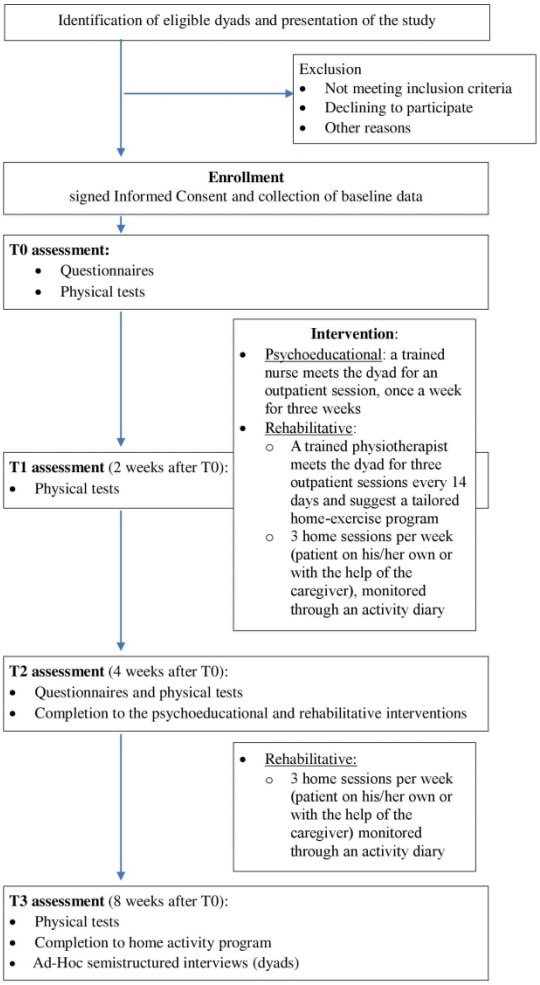


Figure 1. Timeline of assessments and intervention

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | ___title page, 1___ |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 3_____ |
| | 2b | All items from the World Health Organization Trial Registration Data Set | _____ |
| Protocol version | 3 | Date and version identifier | _____ |
| Funding | 4 | Sources and types of financial, material, and other support | 23,24_____ |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 23,24__ |
| | 5b | Name and contact information for the trial sponsor | _____ |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 16,17_____ |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | _____ |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4-7_____ |
| | 6b | Explanation for choice of comparators | _____ |
| Objectives | 7 | Specific objectives or hypotheses | 7_____ |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 7-15_____ |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7_____ |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 7,8_____ |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 8-12_____ |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | _____ |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 10,11 (table 1) |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 11,12____ |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 12-15_____ |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | _pg.11, table 1 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 7-16____ |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 7,8_____ |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | _____ |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | _____ |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | _____ |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | _____ |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | _____ |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 11-14, (table 1) |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 11_____ |

| | | | |
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| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 12 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 16 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | _3,17 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | _16,17_____ |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | _____ |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | _17_____ |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 23_____ |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | _16-17_____ |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | _____ |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | _3,16,17_____ |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | _____ |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | _____ |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | _____ |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | _____ |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.