REVIEW

Journal of Cachexia, Sarcopenia and Muscle (2023)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.13321

Physical function endpoints in cancer cachexia clinical trials: Systematic Review 1 of the cachexia endpoints series

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Abstract

In cancer cachexia trials, measures of physical function are commonly used as endpoints. For drug trials to obtain regulatory approval, efficacy in physical function endpoints may be needed alongside other measures. However, it is not clear which physical function endpoints should be used. The aim of this systematic review was to assess the frequency and diversity of physical function endpoints in cancer cachexia trials. Following a comprehensive electronic literature search of MEDLINE, Embase and Cochrane (1990–2021), records were retrieved. Eligible trials met the following criteria: adults (≥18 years), controlled design, more than 40 participants, use of a cachexia intervention for more than 14 days and use of a physical function endpoint. Physical function measures were classified as an objective measure (hand grip strength [HGS], stair climb power [SCP], timed up and go [TUG] test, 6-min walking test [6MWT] and short physical performance battery [SPPB]), clinician assessment of function (Karnofsky Performance Status [KPS] or Eastern Cooperative Oncology Group-Performance Status [ECOG-PS]) or patient-reported outcomes (physical function subscale of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaires [EORTC QLQ-C30 or C15]). Data extraction was performed using Covidence and followed PRISMA guidance (PROSPERO registration: CRD42022276710). A total of 5975 potential studies were examined and 71 were eligible. Pharmacological interventions were assessed in 38 trials (54%). Of these, 11 (29%, $n = 1184$) examined megestrol and 5 (13%, $n = 1928$) examined anamorelin; nutritional interventions were assessed in 21 trials (30%); and exercise-based interventions were assessed in 6 trials (8%). The remaining six trials (8%) assessed multimodal interventions. Among the objective measures of physical function (assessed as primary or secondary endpoints), HGS was most commonly examined (33 trials, $n = 5081$) and demonstrated a statistically significant finding in 12 (36%) trials ($n = 2091$). The 6MWT was assessed in 12 trials ($n = 1074$) and was statistically significant in 4 (33%) trials ($n = 403$), whereas SCP, TUG and SPPB were each assessed in 3 trials. KPS was more commonly assessed than the newer ECOG-PS (16 vs. 9 trials), and patient-reported EORTC QLQ-C30 physical function was reported in 25 trials. HGS is the most commonly used physical function endpoint in cancer cachexia clinical trials. However, heterogeneity in study design, populations, intervention and endpoint selection make it difficult to comment on the optimal endpoint and how to measure this. We offer several recommendations/considerations to improve the design of future clinical trials in cancer cachexia.

Keywords cachexia; cancer; endpoints; physical function; trials

Received: 5 May 2023; Revised: 19 June 2023; Accepted: 2 August 2023
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Introduction

It is well established in oncology that a person's physical function is a critical component of physiological reserves and guides their assessment and management. This is best evidenced by the use of performance status (PS), which routinely informs decision making and is a robust indicator for survival and treatment stratification. PS also indicates the extent to which a patient is limited in terms of their ability to perform activities of daily living.

Since 1947, PS has been assessed using the Karnofsky Performance Status (KPS), a percentage score of physical function that is determined by the patient's clinician. KPS, however, has largely been superseded by the Eastern Cooperative Oncology Group-Performance Status criteria (ECOG-PS) since 1982, and is a reliable measure of physical functioning, prognosis and overall disease burden, and correlates highly with quality of life.[1,2] ECOG-PS is easier to measure, has comparable sensitivity and specificity to KPS and is now used extensively in cancer care. Despite this, the role of measures of PS in cancer cachexia as a diagnostic criterion and/or outcome in clinical trials has not been reported.

Fearon and colleagues published a new consensus definition of cachexia in 2011. They proposed that cancer cachexia is a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.[3] In view of this complex definition, researchers are divided on how the syndrome is best assessed and have proposed various approaches that include physical, biochemical and patient-reported measures. Considering the role of PS in cachexia, Fearon et al. also noted that the measure was applicable in the refractory component, helping to identify those patients who are nearing the end of life.[3] In addition, ECOG-PS has also been shown to be superior to measures of lean mass and nutritional intake in terms of survival prediction.[4–6]

The 2011 definition of cachexia raises an important question about how cancer cachexia is defined and therefore measured, particularly in the context of clinical trials. Regulatory bodies such as the Food and Drug Administration (FDA) now require that endpoints, be they patient-reported outcome measures (PROMs), clinician-determined or performance-based measures, should be related to how a patient feels, functions or lives/survives.[7] Cachexia trials may focus on different aspects such as anorexia or quality of life and thus should use endpoints related to the potential mechanism of action of an intervention. For therapies that improve lean muscle mass, these should also demonstrate improvements in function.[8]

Cachexia trials have used a variety of different endpoints that aim to demonstrate changes in physical function. These may be categorized as assessments that are physician determined (e.g., ECOG-PS and KPS), reported by patients (e.g., functional subscales of quality of life assessments) or objective measures of physical function. The latter is the most diverse group and, among others, includes 'hand grip strength' (HGS), the 'timed up and go' (TUG) test, the '6-min walking test' (6MWT), the 'stair climb power' (SCP) test and the 'short physical performance battery' (SPPB).[9]

With such diversity in measures of physical function comes the challenge of interpreting clinical benefit of results from cachexia trials. Until there is an appraisal of the myriad of physical function endpoints and their use in cachexia, researchers will not be able to draw meaningful conclusions from their results. It is therefore imperative that cachexia researchers now take stock of what has been done and, more importantly, what may be meaningful.

The aim of this systematic review was to outline the frequency and diversity of physical function measures that are used in cancer cachexia trials. It is part of a series of reviews that examine a variety of endpoints used in cancer cachexia trials.

Methods

This systematic review was reported as described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[10]

Search strategy

The search for studies published from January 1990 until 2 June 2021 was conducted by a research librarian (University of Oslo, Norway) using the databases MEDLINE (Ovid), Embase (Ovid) and Cochrane Central Register of Controlled Trials (*Appendix S1*). It was registered on the International Prospective Register of Systematic Reviews (PROSPERO registration: CRD42022276710) where further detail is available.[11]

Eligibility criteria

Articles were considered eligible if they were controlled trials investigating interventions that aim to treat or attenuate cachexia and associated conditions (as defined in the PROSPERO register) in adult patients with cancer. There were no restrictions in the type of intervention (pharmacological, nutritional, exercise, multimodal etc.) nor the type of comparator. To reduce bias and focus on outcomes with most clinical impact, articles were excluded if the study included fewer than 40 patients and/or the intervention lasted $<$14 days. Studies were included if they were published in full text from 1990 and were written in English.

Data selection and extraction

This systematic review is part of a comprehensive collaboration including reviews examining different endpoints in cachexia (body composition, oncology, physical function, PROMs, systemic inflammation and nutritional). As most controlled trials in cachexia explore several different endpoints (as primary or secondary), articles were divided evenly among the review team for data extraction.

All articles identified were transferred to Covidence software.[12] Article selection based on titles was carried out by two independent reviewers (O. D. and B. L.). Articles selected by their titles had their abstracts read and selected by two independent reviewers (T. S. S. and B. L.). Any uncertainties in assessing the eligibility of the studies were discussed among the authors until a consensus was reached.

A data extraction table was developed, pilot-tested and refined within the review group before data were extracted from each article by two independent authors from the review group. Articles relevant to each systematic review were then identified from the data. For this review, relevant articles were those that assessed the specified physical function endpoints noted in this review.

Assessing risk of bias

The methodological quality of each study was systematically assessed by four independent reviewers (J. M., J. S., O. D. and B. L.) using the modified Downs and Black checklist.[13] Among other criteria, the tool assesses study design, external and internal validity, estimate of variance reporting and whether the outcome was defined and robust.

Endpoints

Endpoints investigated in this review were measures of physical function in cancer cachexia. These included objective assessments of physical function: HGS,[14] 6MWT,[15] SCP,[16] SPPB[17] and TUG.[18] The review also included measures of physical function that are assessed by clinicians (ECOG-PS and KPS) and patient-reported assessments of physical function (physical function subscales of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaires [EORTC QLQ-C30]).[19]

Data analysis

As expected, the retrieved studies were heterogeneous in terms of interventions and patient characteristics, and the variety of outcome measures studied large. As such, meta-analysis of the effect of the interventions was not relevant, and these data were summarized narratively. In studies where the sample size was more than 100, raw data on objective measures and corresponding variability of measures were extracted and presented in keeping with PRISMA guidelines.[10]

Results

After removal of duplicates, 5975 records were reviewed by title or abstract (the abstract was assessed where the title was insufficient), resulting in 369 records being appraised in full. Following appraisal, 250 records were further excluded, leaving 116 that were eligible for the systematic review database. Of these, 71 studies examined physical function endpoints and thus were eligible to be included in the review. This is detailed in *Figure 1*.

The key characteristics of eligible trials are presented in *Table 1*. As predicted, the trials were heterogeneous in terms of intervention and tumour site studied. Trials also varied in sample size from n = 40 to n = 929 patients. Pharmacological interventions were assessed in 38 (54%) trials, and of these, 11 (29%) examined megestrol (n = 1184) and 5 (13%) examined anamorelin (n = 1928). Twenty-one (30%) trials examined nutritional interventions (n = 2340), six (8%) trials examined exercise-based interventions (n = 430) and six (8%) trials examined combination/multimodal interventions (n = 1422).

DOI: 10.1002/jcsm.13321

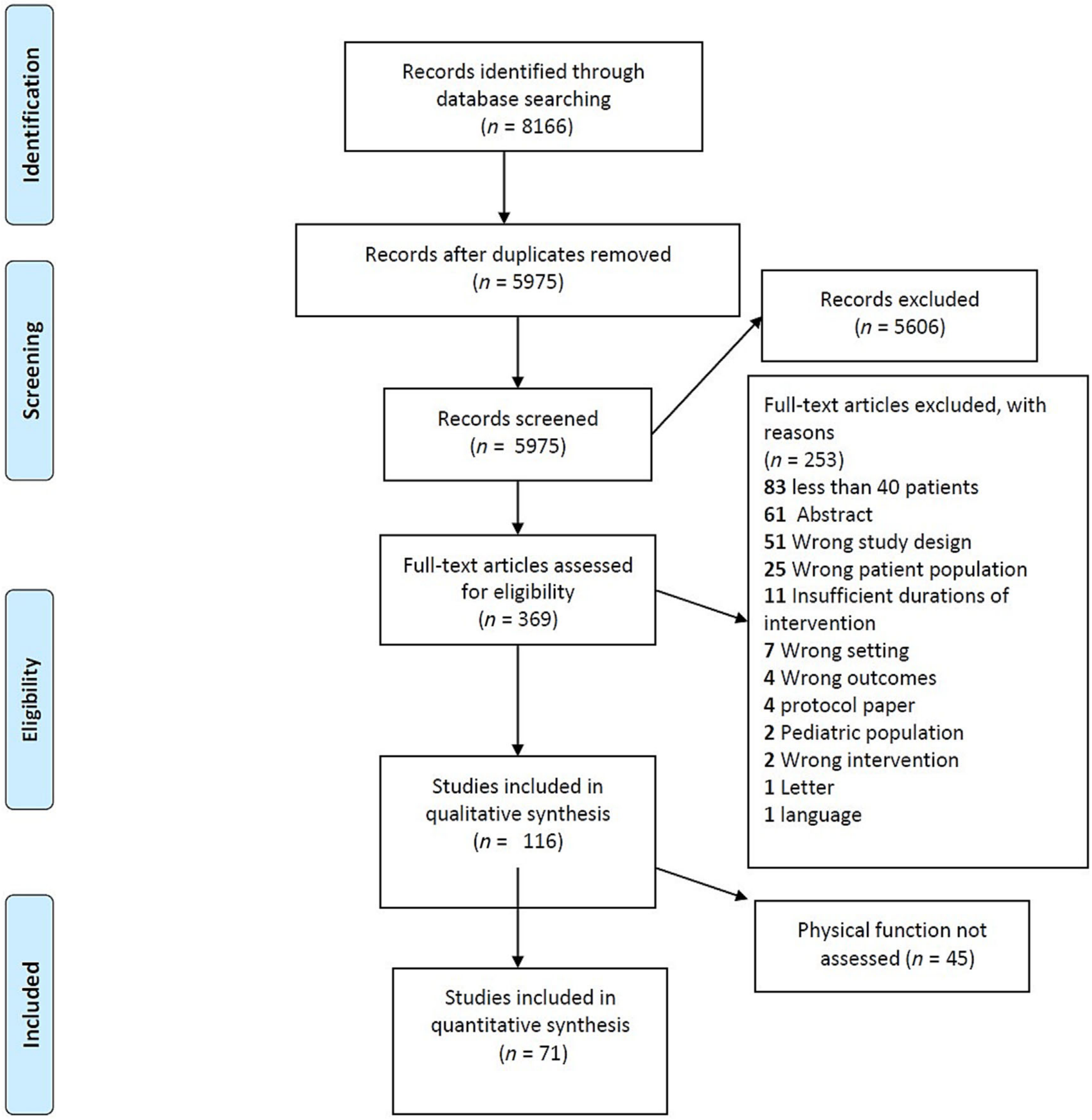

FIGURE 1 PRISMA flowchart.

In total, measures of physical function were used as a primary endpoint in 21 (30%) trials. Such measures include objective measures of physical function (HGS, 6MWT, TUG, SCP and SPPB), clinician assessment of function (ECOG-PS and KPS), which were each used in 7 (10%) trials, and PROMs of physical function (EORTC QLQ-C30 physical function [PF] subscale) in 10 (14%) trials. The remainder of the studies used physical function measures as secondary endpoints. Where primary and secondary endpoints were not clear, all outcomes were assumed to be secondary.

Table 2 summarizes the number and combined size of eligible trials that report each functional endpoint. Of note, HGS was examined in 33 trials (*n* = 5081) and demonstrated a statistically significant finding in 12 (36%) trials (*n* = 2099). The 6MWT was assessed in 12 trials (*n* = 1074) and demonstrated a statistically significant finding in 4 (36%) trials (*n* = 403). SCP, TUG and SPPB were each assessed in three trials (*n* = 371, 279 and 320, respectively). For clinician assessment of function, statistically significant changes in ECOG-PS were noted in 7 out of 9 (78%, *n* = 890) studies, while statistically significant changes in KPS were noted in 5 out of 16 studies (32%, *n* = 711). For patient-reported assessments of function, the physical function subscale of the EORTC QLQ-C30 was statistically significant in 11 out of 25 trials (44%, *n* = 1794).

Figure 2 shows the relationship between study interventions and functional measures across eligible trials. Most

DOI: 10.1002/jcsm.13321

Table 1 Key characteristics of eligible trials

Year	Author	Quality	Design	*n*	Cancer	Intervention	Comparator	Primary outcome	Function measure[a]
2022	Kutz[20]	7	RCT	58	Head and neck	Individual nutritional counselling	Usual standard of care	EORTC QLQ-C30	**EORTC QLQ-C30-PF**
2021	Currow[21]	6	RCT	190	Mixed	Megestrol acetate + dexamethasone	Placebo	Appetite	KPS
2021	Hunter[22]	7	RCT	120	Mixed	Mirtazapine	Placebo	Appetite	HGS
2021	Tobberup[23]	9	RCT	120	Lung	Dietary counselling/fish oil	Usual standard of care	Feasibility, compliance, PG-SGA SF, weight, skeletal muscle, measures of physical function	TUG
2020	Famil-Dardashti[24]	8	RCT	47	Mixed	Herbal combination	Placebo + megestrol	Weight gain	**HGS** + ECOG-PS
2020	Balstad[25]	8	RCT	40	Mixed	Multimodal	Usual standard of care	Feasibility	HGS
2020	Movahed[26]	8	RCT	100	Gastrointestinal	Individual nutritional therapy	General dietary advice	PG-SGA	HGS
2020	Qiu[27]	6	RCT	96	Lung	Artificial nutrition	Usual standard of care	Nutritional status, EORTC QLQ-C30, incidence of complications	**EORTC QLQ-C30-PF**
2020	Hong[28]	9	RCT	190	Mixed	Machine-based resistance exercise	Progressive muscle relaxation	Multiple	**EORTC QLQ-C30-PF**
2020	Kamel[29]	7	RCT	40	Pancreatic	Resistance exercise	Usual standard of care	Mobility, muscle strength, lean body mass	**6MWT**, **400-m walk**, **chair rise**
2020	Storck[30]	10	RCT	52	Mixed	Multimodal	Usual standard of care	SPPB	SPPB, **HGS**, TUG
2020	Bouleuc[31]	7	RCT	111	Mixed	Parenteral nutrition with provitamins, trace elements and electrolytes	Oral feeding	EORTC QLQ-C15-PAL, deterioration-free survival	**ECOG-PS**
2020	Dehghani[32]	7	RCT	40	Gastrointestinal	Captopril	Placebo	EORTC QLQ-C30	**EORTC QLQ-C30-PF**
2019	Cereda[33]	8	RCT	166	Mixed	Nutritional counselling + whey	Nutritional counselling	Phase angle	**HGS**
2019	Obling[34]	7	RCT	47	Mixed	Home parenteral nutrition	Usual standard of care	Fat-free mass	HGS, 6MWT
2019	Laviano[35]	8	RCT	55	Lung	Supplement with protein + carbohydrate	Isocaloric supplement	Adverse events, clinical signs, changes in medication, routine blood tests	HGS
2019	Stuecher[36]	8	RCT	44	Mixed	Walking	Usual standard of care	SPPB	SPPB
2019	Wiskemann[37]	5	RCT	43	Pancreatic	Supervised resistance training	Usual standard of care	Feasibility, effectiveness, muscle strength CPET, 6MWT	6MWT
2018	Katakami[38]	8	RCT	174	Lung	Anamorelin	Placebo	Lean body mass	**HGS**, 6MWT
2018	Kouchaki[39]	8	RCT	90	Mixed	Megestrol acetate + celecoxib	Megestrol acetate + placebo	Weight	**HGS**, **ECOG-PS**
2018	Britton[40]	8	RCT	307	Head and neck	Multimodal	Usual standard of care	PG-SGA	**EORTC QLQ-C30-PF**
2018	Golan[41]	7	RCT	125	Pancreatic	Trial drug	Placebo	Survival	HGS, SCP, **6MWT**, TUG
2018	Xie[42]	8	RCT	54	Lung	Thalidomide + cinobufagin	Usual standard of care	Arm circumference, weight, albumin, EORTC QLQ-C30, side effects, HGS	**HGS**

(*Continues*)

Table 1 (continued)

Year	Author	Quality	Design	*n*	Cancer	Intervention	Comparator	Primary outcome	Function measure[a]
2018	Schink[43]	9	CT	131	Mixed	Supervised physical exercise + nutritional advice	Nutritional advice only	Skeletal muscle mass	HGS, EORTC QLQ-C30, **6MWT**, **KPS**
2018	Uster[44]	9	RCT	58	Mixed	Multimodal	Usual standard of care	Global health status, EORTC QLQ-C30	EORTC QLQ-C30-PF, HGS, 6MWT
2018	Turcott[45]	7	RCT	33	Lung	Nabilone	Placebo	FAACT	EORTC QLQ-C30-PF
2017	Jatoi[46]	8	RCT	263	Mixed	Creatine	Placebo	Weight gain	HGS
2017	Currow[47]	8	RCT	513	Lung	Anamorelin	Placebo	Safety, tolerability	HGS
2017	Leedo[48]	8	RCT	40	Lung	Delivery of protein-rich meals	Usual standard of care	EORTC QLQ-C30	**ECOG**, HGS
2017	Solheim[49]	8	RCT	41	Mixed	Multimodal	Usual standard of care	Feasibility	6MWT, HGS
2017	Werner[50]	7	RCT	33	Pancreatic	Fish oil	Marine phospholipids	Weight, appetite	EORTC QLQ-C30-PF
2017	Zietarska[51]	6	RCT	95	Colorectal	Oral nutritional supplement	Usual standard of care	Treatment toxicity	KPS
2016	Takayama[52]	8	RCT	180	Lung	Anamorelin	Placebo	Lean body mass, HGS	HGS, **KPS**
2016	Temel[53]	8	RCT	979	Lung	Anamorelin	Placebo	Lean body mass, HGS	HGS
2016	Gavazzi[54]	7	RCT	79	Mixed	Home enteral nutrition	Nutritional counselling	Weight	HGS, KPS
2016	Woo[55]	9	RCT	67	Pancreatic	Pancreatic exocrine replacement therapy	Usual standard of care	Body weight	EORTC QLQ-C30-PF
2016	Coats[56]	10	RCT	87	Mixed	Espindolol	Placebo	Rate of weight change	**HGS**, SCP, SPPB, **6MWT**
2016	Capozzi[57]	8	RCT	60	Mixed	Immediate lifestyle intervention	Delayed lifestyle intervention	Body composition	6MWT
2015	Focan[58]	7	RCT	53	Mixed	Mindfulness/dietician	Usual standard of care	Weight loss, BMI, ECOG-PS, EORTC QLQ-C30, total daily calorie intake, FFMQ, satisfaction with intervention	EORTC QLQ-C30-PF
2015	Garcia[59]	7	RCT	82	Mixed	Anamorelin	Placebo	Lean body mass	**HGS**
2014	Hong[60]	8	Phase I	52	Mixed	Monoclonal antibody	Dose comparison	Safety, tolerability	ECOG-PS, EORTC QLQ-C30-PF
2014	Poulsen[61]	5	RCT	61	Mixed	Multimodal	Usual standard of care	Weight	**EORTC QLQ-C30-PF**
2014	Pottel[62]	8	RCT	85	Head and neck	Echium oil	Usual standard of care	Weight loss	EORTC QLQ-C30-PF, **HGS**
2013	Dobrila-Dintinjana[63]	7	RCT	628	Gastrointestinal	Multimodal	Usual standard of care	Nutritional status, BMI, Nottingham Screening Tool, ECOG-PS	ECOG-PS
2013	Dobs[64]	8	RCT	159	Mixed	Enobosarm	Placebo	Lean body mass	6MWT, HGS + **SCP**
2012	Maccio[65]	8	RCT	124	Gynaecological	Multimodal	Megestrol acetate	Lean body mass, REE	HGS + **ECOG-PS**
2012	Kraft[66]	10	RCT	72	Pancreatic	L-Carnitine	Placebo	Weight, adverse events, BIA, EORTC QLQ-C30, BFI questionnaire, survival	EORTC QLQ-C30-PF
2012	Wen[67]	5	RCT	93	Mixed	Megestrol acetate + thalidomide	Megestrol acetate	Weight, fatigue (MFSI-SF scale), quality of life (EORTC QLQ-C30), safety, adverse events	**ECOG-PS**, **HGS**

(*Continues*)

Table 1 (continued)

Year	Author	Quality	Design	*n*	Cancer	Intervention	Comparator	Primary outcome	Function measure[a]
2012	Madeddu[68]	7	RCT	60	Mixed	L-Carnitine + celecoxib + megestrol acetate	L-Carnitine + celecoxib	Lean body mass, daily physical activity	HGS, **6MWT**
2011	Baldwin[69]	8	RCT	358	Mixed	Multimodal	Nutritional encouragement	Survival	HGS
2011	Silander[70]	6	RCT	134	Mixed	PEG feeding before treatment + individual nutritional support	Usual standard of care	Weight loss	**EORTC QLQ-C30-PF**
2010	Mantovani[71]	7	RCT	332	Mixed	Multiple (five arms)	Multiple	Lean body mass, REE, fatigue	HGS, **ECOG-PS**, EORTC QLQ-C30-PF
2008	Wiedenmann[72]	7	RCT	89	Pancreatic	Infliximab	Placebo	Lean body mass	6MWT, **KPS**
2006	Fearon[73]	8	RCT	518	Mixed	Eicosapentaenoic acid supplement	Placebo	Weight	KPS, **EORTC QLQ-C30-PF**
2005	Ravasco[74]	7	RCT	75	Head and neck	Nutritional supplements + nutritional counselling	Nutritional supplements	PG-SGA, energy intake	**EORTC QLQ-C30-PF**
2005	Gordon[75]	10	RCT	50	Pancreatic	Thalidomide	Placebo	Weight	HGS, EORTC QLQ-C30-PF
2004	Isenring[76]	8	RCT	60	Mixed	Intensive nutritional counselling	Usual standard of care	Weight, free-fat mass, PG-SGA, EORTC QLQ-C30	**EORTC QLQ-C30-PF**
2003	Fearon[77]	8	RCT	200	Pancreatic	Oral supplement + N-3 fatty acid	Oral supplement	KPS, EORTC QLQ-C30, energy intake, protein Intake	KPS, EORTC QLQ-C30-PF
2003	Bruera[78]	7	RCT	60	Mixed	Multimodal	Placebo	Appetite	KPS
2000	Erkurt[79]	8	RCT	100	Mixed	Megestrol acetate	Usual standard of care	Weight, ECOG-PS, appetite, malnutrition, loss of taste and smell	**ECOG-PS**
1999	McMillan[80]	7	RCT	73	Mixed	Megestrol acetate + ibuprofen	Placebo	Weight gain, QoL	EORTC QLQ-C30-PF
1999	Westman[81]	7	RCT	255	Mixed	Megestrol acetate	Placebo	Quality of life: EORTC QLQ-C30	**EORTC QLQ-C30-PF**
1998	Catalina[82]	5	RCT	107	Mixed	Megestrol acetate (low dose)	Megestrol acetate (high dose)	Weight, nutritional status, quality of life, KPS	KPS
1998	De Conno[83]	6	RCT	42	Mixed	Megestrol acetate	Placebo	Appetite	KPS
1997	Neri[84]	4	RCT	225	Mixed	Medroxyprogesterone acetate	Usual standard of care	Multiple patient-reported outcomes	**KPS**
1996	Lissoni[85]	7	RCT	86	Mixed	Supportive care + melatonin	Supportive care	Weight loss, TNF	**KPS**
1996	Gebbia[86]	6	RCT	122	Mixed	Megestrol acetate	Dose comparison	Appetite, weight, food intake, KPS, extension PS, pain, energy, depression, survival, toxicity	KPS
1996	Simons[87]	7	RCT	134	Mixed	Medroxyprogesterone acetate	Placebo	Appetite, weight	EORTC QLQ-C30-PF

(*Continues*)

DOI: 10.1002/jcsm.13321

Table 1 (continued)

Year	Author	Quality	Design	*n*	Cancer	Intervention	Comparator	Primary outcome	Function measure[a]
1994	Lai[88]	5	RCT	52	Mixed	Megestrol acetate + prednisolone	Placebo	Appetite, weight, KPS, tolerance to radiation, anorexia management	KPS
1993	Downer[89]	1	RCT	60	Mixed	Medroxyprogesterone acetate	Placebo	Appetite, weight, mid-arm circumference, triceps skin fold	KPS

Abbreviations: 6MWT, 6-min walking test; BFI, Big Five Inventory; BIA, bioelectrical impedance analysis; BMI, body mass index; CPET, cardiopulmonary exercise test; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; EORTC QLQ-C30-PF, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaires physical function; FAACT, Functional Assessment of Anorexia/Cachexia Therapy; FFMQ, Five-Facet Mindfulness Questionnaire; HGS, hand grip strength; KPS, Karnofsky Performance Status; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form; PEG, percutaneous endoscopic gastrostomy; PG-SGA SF, Patient-Generated Subjective Global Assessment Short Form; QoL, quality of life; RCT, randomized controlled trial; REE, resting energy expenditure; SCP, stair climb power; SPPB, short physical performance battery; TNF, tumour necrosis factor; TUG, timed up and go test.
[a]Where functional measure is in bold, this denotes a significant finding.

studies assessed pharmacological interventions, followed by nutritional intervention and then exercise/lifestyle and multimodal interventions. HGS was assessed most commonly, particularly in the larger trials and in those where a pharmaceutical intervention was assessed.

These aggregated data do not allow us to assess which measurements are more useful in terms of being an accurate reflection of physical functioning or their sensitivity to changes in functioning. However, we explored the relationships between specific endpoints looking at the 29 studies that report more than one measure of physical function. HGS reported was one of the measures in 25 of these studies and most commonly assessed together with 6MWT (k = 9), ECOG-PS (k = 5), KPS (k = 5) or EORTC-PF (k = 5) (*Table 3* and *Figure 3*).

In *Table 3*, we summarize the number of studies that identified statistically significant effects of one, both or neither measure of physical function for each pair of measures. While it was common that both HGS and the other measures of physical function were found to be either statistically significant or not in these trials, 6MWT, ECOG-PS and KPS were more often statistically significant in trials where HGS was reported not to be statistically significant (*Table 3*). It was of interest that HGS generally decreased in the intervention and also in the control groups of the reported trials, although in two cases, the intervention group had stable or improved HGS, respectively. Where the 6MWT was assessed, there was no discernible difference between the control and intervention groups. Limited inference can be drawn from these observations; however, the effect of any cachexia intervention could be to attenuate decline and clearly may be dependent on the population being examined.

Table S1 details the raw values of HGS, 6MWT and TUG in selected two arm trials ($n \geq 100$) where these were reported. All trials were pharmacological interventions including studies of anamorelin, enobosarm and antimyostatin therapies. There were no trials where either SPPB or SCP was assessed in which the sample size was more than 100. These data demonstrate that raw values were broadly comparable although there was a limit to data reported.

Table S2 details the raw values of HGS, 6MWT and TUG in selected multi-arm trials ($n \geq 100$). Little inference can be made from these data as only a small number of trials used a multi-arm design.

Of the 71 studies examining physical function included in this review, 27 were designed as randomized trials that included a placebo control group. The details of these studies are presented in *Table S3*. As the risk of bias is lower in this group, a subset analysis of the randomized, placebo-controlled studies was performed, with results presented in *Table S4*. These studies included a total of 4594 participants. Broadly, functional endpoints demonstrated results with statistical significance at a similar proportion as in the overall cohort, but analysis is limited by the small sample sizes for each functional endpoint.

Table 2 Frequency of use of functional endpoints in eligible trials

Endpoint	Number of studies	Year published	Total sample size	Type of intervention	Studies with statistically significant results: Number of studies (percentage of studies)	Sample size (percentage of total sample size)	Type of intervention
Objective measures of physical function							
Hand grip strength	33	1998–2021	5081	Pharmacological: 20 Nutritional: 8 Exercise/lifestyle[a]: 0 Multimodal: 5	12 (36%)	2099 (41%)	Pharmacological: 9 Nutritional: 2 Exercise/lifestyle[a]: 0 Multimodal: 1
Six-minute walking test	12	2008–2019	1074	Pharmacological: 6 Nutritional: 1 Exercise/lifestyle[a]: 2 Multimodal: 3	4 (33%)	403 (38%)	Pharmacological: 1 Nutritional: 0 Exercise/lifestyle[a]: 0 Multimodal: 3
Stair climb power	3	2013–2018	371	Pharmacological: 3 Nutritional: 0 Exercise/lifestyle[a]: 0 Multimodal: 0	1 (33%)	159 (43%)	Pharmacological: 1 Nutritional: 0 Exercise/lifestyle[a]: 0 Multimodal: 0
Timed 'up and go' test	3	2018–2020	279	Pharmacological: 1 Nutritional: 1 Exercise/lifestyle[a]: 0 Multimodal: 1	0 (0.00%)	0 (0.00%)	Pharmacological: 0 Nutritional: 0 Exercise/lifestyle[a]: 0 Multimodal: 0
SPPB	3	2016–2020	320	Pharmacological: 1 Nutritional: 0 Exercise/lifestyle[a]: 1 Multimodal: 1	0 (0.00%)	0 (0.00%)	Pharmacological: 0 Nutritional: 0 Exercise/lifestyle[a]: 0 Multimodal: 0
Clinician-assessed measures of physical function							
ECOG	9	2000–2020	1570	Pharmacological: 7 Nutritional: 2 Exercise/lifestyle[a]: 0 Multimodal: 0	7 (78%)	890 (57%)	Pharmacological: 4 Nutritional: 2 Exercise/lifestyle[a]: 0 Multimodal: 1
KPS	16	1993–2021	2236	Pharmacological: 11 Nutritional: 6 Exercise/lifestyle[a]: 0 Multimodal: 1	5 (31%)	711 (32%)	Pharmacological: 4 Nutritional: 0 Exercise/lifestyle[a]: 0 Multimodal: 1
ECOG + KPS	25	1993–2021	2806	Pharmacological: 18 Nutritional: 6 Exercise/lifestyle[a]: 0 Multimodal: 1	12 (48%)	1601 (57%)	Pharmacological: 8 Nutritional: 2 Exercise/lifestyle[a]: 0 Multimodal: 2
PROMs of physical function							
EORTC QLQ-C30 physical function	25	1996–2022	3167	Pharmacological: 11 Nutritional: 10 Exercise/lifestyle[a]: 2 Multimodal: 2	11 (44%)	1794 (57%)	Pharmacological: 3 Nutritional: 7 Exercise/lifestyle[a]: 1 Multimodal: 0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaires; KPS, Karnofsky Performance Status; PROMs, patient-reported outcome measures; SPPB, short physical performance battery.
[a]Lifestyle measures varied and included walking, behavioural changes and so forth.

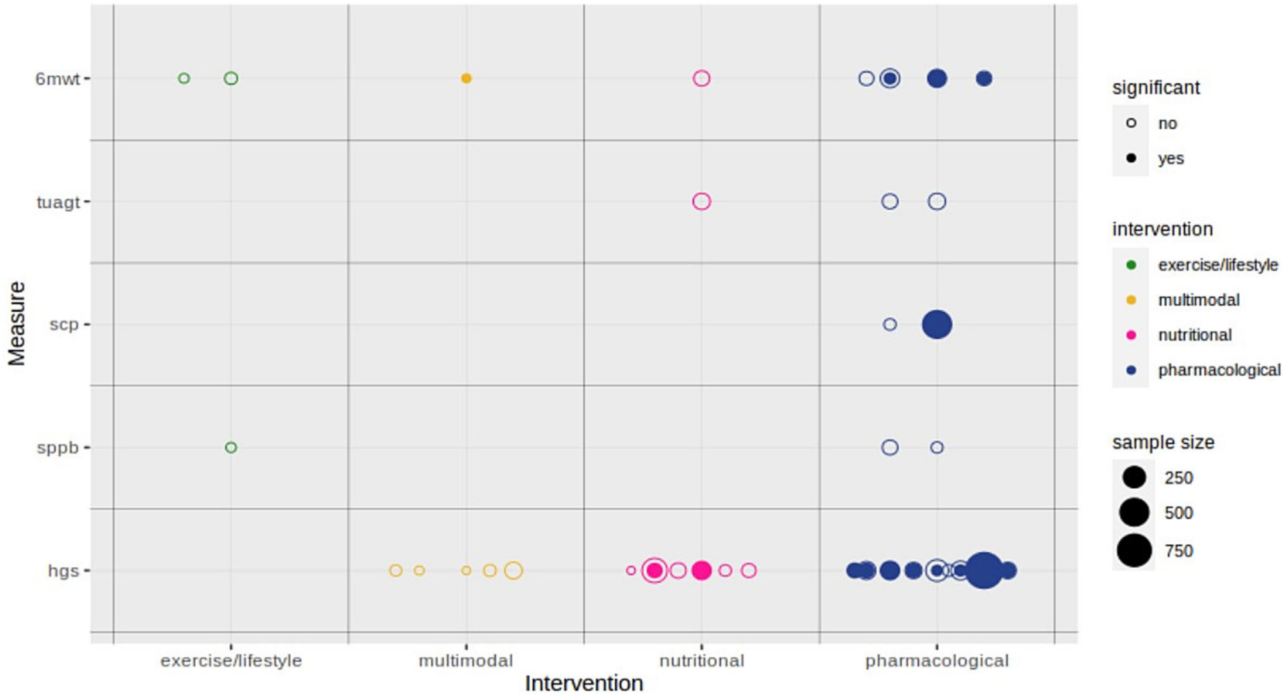

FIGURE 2 The relationship between study interventions and functional measures across eligible trials. 6MWT, 6-min walking test; HGS, hand grip strength; SCP, stair climb power; SPPB, short physical performance battery; TUG, timed up and go test.

Table 3 Pairs of measures of physical function reported in included studies

		Number of studies				
Measure 1	Measure 2	Assessing both measures	Both measures statistically significant	Measure 1 statistically significant	Measure 2 statistically significant	Neither measure statistically significant
HGS	6MWT	9	1	1	3	4
HGS	ECOG-PS	5	2	0	3	0
HGS	KPS	5	0	1	2	2
HGS	EORTC-PF	5	0	1	0	4
HGS	SCP	3	0	1	1	1
6MWT	SCP	3	0	2	1	0
EORTC-PF	KPS	3	0	1	1	1
EORTC-PF	ECOG-PS	2	0	0	1	1
EORTC-PF	6MWT	2	0	0	1	1
HGS	SPPB	2	0	2	0	0
HGS	TUG	2	0	1	0	1
KPS	6MWT	2	1	1	0	0
SCP	SPPB	1	0	0	0	1
SCP	TUG	1	0	0	0	1
6MWT	SPPB	1	0	1	0	0
6MWT	TUG	1	0	1	0	0
TUG	SPPB	1	0	0	0	1

Abbreviations: 6MWT, 6-min walking test; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; EORTC-PF, European Organisation for the Research and Treatment of Cancer physical function; HGS, hand grip strength; KPS, Karnofsky Performance Status; SCP, stair climb power; SPPB, short physical performance battery; TUG, timed up and go test.

Discussion

This is the first systematic review of physical function endpoints in clinical trials examining interventions for cancer cachexia. It was noted that a broad range of interventions showed varying levels of efficacy, assessed with different outcome measures. Objective measures such as HGS and, to a lesser extent, the 6MWT have been studied in the largest trials, usually in the context of a pharmacological intervention.

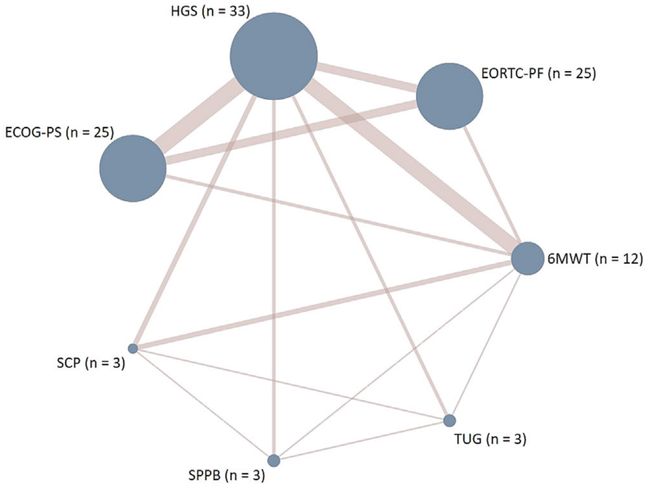

FIGURE 3 Network diagram of the reporting of physical function measures in included trials. Size of nodes reflects the number of studies reporting each measure and the thickness of the connecting edges reflects the number of studies reporting each pair of measures (numerical details found in *Table 3*). 6MWT, 6-min walking test; ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; EORTC-PF, European Organisation for the Research and Treatment of Cancer physical function; HGS, hand grip strength; SCP, stair climb power; SPPB, short physical performance battery; TUG, timed up and go test.

Objective measures of physical function

Among the endpoints assessed in the present review, HGS was assessed in the largest number of studies and had the largest total sample size. The use of HGS is congruent with definitions of cachexia[90] and supports work by Song and co-workers.[91] In over 1400 patients with cancer cachexia, they demonstrated that low HGS at baseline was an independent risk factor for cachexia and associated with reduced 1-year survival. These findings corroborated earlier work by Zhuang and co-workers.[92]

Our results have also identified the 6MWT as a candidate for functional assessment in cachexia. The advantage of it is that it does not require any specialized equipment and may be performed in any healthcare setting. Despite being commonly used as a measure of physical function, there are limited data to support its use in cachexia. LeBlanc and co-workers examined the 2011 consensus definition of cachexia and compared it with key measures including the 6MWT. They failed to show a relationship between cachexia stage and 6MWT.[93] Nonetheless, when assessed alongside other measures of physical function, the 6MWT was more frequently found to be statistically significant. Interpreting this observation cautiously, 6MWT may be more sensitive to changes in physical function, may be impacted by other symptoms such as dyspnoea or have less variability between participants, meaning that smaller changes are associated with greater statistical certainty. Considering that few eligible studies have assessed SCP, TUG and SPPB (three studies each), no firm conclusions can be drawn from our results.

Performance status

Our findings highlighted the potential importance of ECOG-PS in the assessment of cachexia. As mentioned, ECOG-PS has largely succeeded KPS as the measure of PS in cachexia trials, which may be due to fewer categories within the former. We also see in our results that ECOG-PS may be more sensitive to changes in physical function than HGS given that ECOG-PS alone was found to be statistically significant in three of five studies assessing both measures.

Patient-reported measure of physical function

The EORTC QLQ-C30-PF subscale was one of the most widely assessed PROMs in the present review, used in 33 studies. We have, however, focused on those that specifically reported physical function data (EORTC QLQ-C30-PF) (25 studies). With only eight of these studies also assessing another measure of physical function, it is unclear whether changes in objective measures of physical function consistently are reflected in changes in EORTC QLQ-C30-PF. Further studies are needed to determine the relationship between objective and PROMs of physical function, along with an assessment of which approach reflects the most clinically meaningful assessment and how other factors (such as frailty) may impact these. In addition, the relationship between lean mass and function may not be linear and may have a ceiling. Bye and co-workers highlighted this by demonstrating that above a certain cut-off of lean mass, physical function plateaued. Therefore, that relationship between lean mass and physical

DOI: 10.1002/jcsm.13321

function may be dependent on absolute value of the former.[94] Another critical consideration is that different patient-reported measures of physical function assessment may in fact reflect different contexts of day-to-day living and, as such, one size may not fit all.[95]

Implications

It is important to note here that statistical significance, or lack thereof, reflects the degree of effectiveness of the intervention on a particular measure, the variance of that measure and the sample size of the study. Furthermore, statistical significance does not necessarily equate to clinical significance. Ultimately, the choice of outcome measures must be guided by a consensus as to the most clinically important outcome and, where possible, quantitative evidence identifying which measure most accurately reflects this outcome. The most appropriate outcome chosen should reflect the aim and mechanism of the intervention.

While there is an increasing use of functional endpoints in cachexia trials, there is, however, no consensus as to which is the optimal measure to use.[96] Indeed, endpoints are inconsistent across cachexia trials and therefore difficult to translate into clinical practice. This is perhaps best illustrated by the ROMANA trials, which examined anamorelin and used a co-primary endpoint of lean muscle mass and HGS.[53] While the trials showed statistically significant results for lean mass, these did not translate to changes in HGS. It is unsurprising as anamorelin is directed at a receptor on Agouti-related protein (AgRP)/neuropeptide Y (NPY) neurons in the hypothalamus, where its primary activity is to enhance appetite and feeding behaviour, and may not have been a relevant outcome for an appetite stimulant.

In the POWER trials (enobosarm), which used SCP as an endpoint, researchers were then criticized that it is not a pure measure of physical function and may be influenced by other parameters such as cardiovascular disease or osteoarthritis.[97] Similarly, in the other trials, function was measured using step count and results are awaited from trials that are underway regarding the impact on this choice of endpoint.[98,99]

Understanding which endpoints are best used in cachexia trials will help develop appropriate treatments. Presently, there remains a cascade of endpoints that can be used, ranging between mortality, quality of life, exercise capacity, clinician assessment of function and PROMs, which can include measures of physical function. However, some alignment is needed. This matters not only for regulatory approval but also to patients, particularly when endpoints such as HGS have a clear relationship with prognosis.

Regarding the former, regulatory agencies consider cancer cachexia as a seriously debilitating and/or life-threatening condition. For a drug to reach regulatory approval, it must be efficacious and deliver a meaningful therapeutic effect,[100] which could be changes in lean mass and/or functional capacity vis-à-vis how a patient feels, forms and functions. Any meaningful change should correlate with morbidity or mortality, be related to the disease, have a plausible biological mechanism of action and be related to baseline function. These criteria lend themselves well to HGS being regarded as core functional assessment in cachexia trials—as either a primary or co-primary endpoint. HGS is widely established as being an indicator of muscle strength and general health status, particularly in older people, so the observations of this review are in keeping with this.

Despite the widespread use of HGS, it is notable that other measures including 6MWT and ECOG-PS and KPS were more often found to be statistically significant in trials where HGS was not included. Once again, we cautiously interpret these findings to suggest that these other measures may be more sensitive to changes in physical function, have a lower variability and/or be a reflection of the multiple morbidities that may be present in populations with cancer cachexia. In sarcopenia (as in cachexia), HGS is well recognized for its excellent screening/diagnostic use,[101] but sarcopenia trials have shifted away from using it as an endpoint as it is similarly inconsistent or nonresponsive to interventions.[102] Variability in HGS may in part be due to the lack of standardized protocols.[103] Key to this would be powering trials to this endpoint, and understanding the minimal clinically important difference (MCID) needs to be taken into account. To date, establishing the MCID for grip strength remains a priority. Bohannon conducted a systematic review to answer this. However, as only four studies were eligible, it was difficult to reach firm conclusions.[104] Despite this, he proposed that a change of 5.0–6.5 kg would represent a meaningful change in HGS.

Often, in clinical trials in cachexia, measures of lean mass are assessed alongside measures of function. This is based on the hypothesis that improvements in lean mass would translate to changes in physical function. Both the enobosarm (POWER) and anamorelin (ROMANA) trials adopted this approach, though neither showed improvements in function alongside the improvements in lean mass. There may be several reasons why this is the case including the assumption, perhaps wrong, that muscle mass and function have a linear relationship. Ramage and Skipworth propose a sigmoid relationship between muscle mass and physical function where in the early stages of disease, function is preserved in the presence of loss of muscle (akin to pre-cachexia).[105] Yet when more substantial loss of muscle is present, functional decline is accelerated to the points where recovery is challenging (refractory cachexia). It is key therefore that patient populations for trials are chosen appropriately so that interventions targeting muscle mass and function are given the optimal chance to be efficacious.

In keeping with the theme of improving trial endpoints, there is also the opportunity for functional measures to be combined with biomarkers. Using the systemic inflammatory

DOI: 10.1002/jcsm.13321

response as a biomarker would be a good starting point as it is now regarded as being central to the genesis of cancer cachexia and is associated with quality of life and survival.[106] The observations by Song et al. that combining function (HGS) with markers of the systemic inflammatory response has improved utility are of interest and worthy of further exploration.[91] It is also clear that HGS has consistency with ECOG and EORTC-PF both within the clinical trials reviewed and in the literature more generally.[107] HGS may give objective credibility to subjective ECOG-PS and EORTC-PF. This consistency of association and their relationship with survival make HGS, ECOG-PS and EORTC-PF the starting point for the assessment of accelerometer measurements in future studies. It must also be considered that HGS, ECOG-PS and EORTC-PF measure distinctly different elements of physical function and are assessed in different ways. Therefore, it may not be appropriate to assign superiority and may depend upon the intervention and the goal/aim of the intervention.

It is challenging to compare the prognostic utility of different physical functional tests as rarely have these been compared in the same population. ECOG-PS remains the most widely assessed and validated prognostic factor across cancer trials[5,108] although HGS has been assessed in a large cohort of patients with cancer cachexia[91]; however, the lack of work examining the other measures in a prognostic capacity does not mean that they are less useful. As well as the prognostic utility of these different measures, another consideration is patient acceptability. HGS is relatively easy to perform with minimal patient burden compared with a 6MWT, for example, which may cause considerable fatigue and may also cause other symptoms (e.g., breathlessness). These aspects will also influence the choice of endpoint in cachexia trials.

For future research, there are also some important design considerations. Detailed baseline characterization of patients, including co-morbidities, is needed, particularly when they may impact on desired study outcomes. Observed trial design issues could be overcome with standardization of protocols of physical function endpoints, appropriate training, certification, monitoring and recertification of staff conducting endpoint assessments. When performance-based, clinician-assessed and patient-assessed measures of physical function are being assessed, it is important that they are aligned with the mechanism of action of the intervention. Emerging digital technologies could also be used to develop better endpoints[109] and are being assessed by the European Medicines Agency.[110]

We posit that the appropriate endpoint(s) should be purposely selected to accurately and meaningfully capture patient-important functional improvements in cancer cachexia. The choice of PRO, PS or PF endpoint (or combination of these endpoints) should also be aligned with the underlying mechanism of action of a specific treatment or intervention. For PF endpoints, particular consideration should be given to what aspect of human performance the test actually measures and how an intervention may need to be specifically tailored to ultimately elicit benefit on the selected PF endpoint. For example, if a study seeks to test the efficacy of an anabolic agent on lower extremity muscle strength or power, then the selection of a specific PF test that accurately assesses lower extremity muscle performance should be considered. Similarly, if investigators seek to utilize an exercise intervention to improve deficits in lower extremity physical performance as determined by the SPPB test, the design of the exercise intervention should have training components that specifically target balance, gait and lower extremity muscle performance impairments.

Strengths and limitations

The review has several strengths. First, a prospective design was adopted (PROSPERO) and a thorough literature search was undertaken including the last three decades of cachexia trials. Second, a robust strategy for appraisal and data extraction was adopted using multiple independent reviewers. Third, we used a validated quality appraisal tool (modified Downs and Black) that enables an appreciation of the quality of included studies to be assessed. Finally, data were presented to allow an appreciation of the broad range of studies and highlight which measures have been used most frequently and with the potential for the greatest sensitivity. A key limitation is that aggregated data do not allow a detailed assessment of the relationship between different measures of physical function and it is therefore not possible to make definitive statements about whether particular measures are preferable because of their accuracy or sensitivity to changes in physical function. Within studies, there were also likely to be significant individual patient differences and there may be an assumption that the cancer is causing weight loss, reduced function and loss of lean mass when it is possible that it may be multifactorial.

Conclusions

This systematic review has examined key measures of physical function in cachexia clinical trials. Multiple measures have been studied and are in use. HGS stands out as being studied most often and provides an important means of comparing results between trials. However, other measures may be more sensitive to changes in physical function.

Conflict of interest statement

S. D. A. has received grants and personal fees from Vifor and Abbott Vascular, and personal fees for consultancies, trial committee work and/or lectures from Actimed, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BioVentrix, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Cytokinetics, Edwards, Farraday Pharmaceuticals, GSK, HeartKinetics, Impulse Dynamics, Novartis, Occlutech, Pfizer, Repairon, Sensible Medical, Servier, Vectorious and V-Wave. He is named co-inventor of two patent applications regarding MR-proANP (DE 102007010834 and DE 102007022367), but he does not benefit personally from the related issued patents. M. F. has received personal fees from Pfizer. M. J.-H. has received funding from CRUK, NIH National Cancer Institute, IASLC International Lung Cancer Foundation, Lung Cancer Research Foundation, Rosetrees Trust, UKI NETs and NIHR. M. J.-H. has consulted for, and is a member of, the Achilles Therapeutics Scientific Advisory Board and Steering Committee, has received speaker honoraria from Pfizer, Astex Pharmaceuticals, Oslo Cancer Cluster and Bristol Myers Squibb and is co-inventor on a European patent application relating to methods to detect lung cancer (PCT/US2017/028013). R. J. E. S. has received personal fees for consultancy from Artelo, Actimed, Faraday and Helsinn; B. L. has received personal fees for consultancy from Artelo, Actimed, Faraday, Kyona Kirin and Toray.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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