Measuring What Is Meaningful in Cancer Cachexia Clinical Trials: A Path Forward With Digital Measures of Real-World Physical Behavior

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ABSTRACT

PURPOSE The burden of cancer cachexia on patients' health-related quality of life, specifically their physical functioning, is well documented, but clinical trials thus far have failed to show meaningful improvement in physical functioning. The purpose of this review is to summarize existing methods of assessing physical function in cancer cachexia, outline a path forward for measuring what is meaningful to patients using digital measures derived from digital health technologies (DHTs), and discuss the current landscape of digital measures from the clinical and regulatory standpoint.

DESIGN For this narrative review, peer-reviewed articles were searched on PubMed, clinical trials records were searched on clinicaltrials.gov, and records of digital measures submitted for regulatory qualification were searched on the US Food and Drug Administration's Drug Development Tool Qualification Program database.

RESULTS There are gaps in assessing aspects of physical function that matter to patients. Existing assessment methods such as patient-reported outcomes and objective performance outcomes have limitations, including their episodic nature and burden to patients. DHTs such as wearable sensors can capture real-world physical behavior continuously, passively, and remotely, and may provide a more comprehensive picture of patients' everyday functioning. Recent regulatory submissions showcase potential clinical implementation of digital measures in various therapeutic areas.

CONCLUSION Digital measures of real-world physical behavior present an opportunity to detect and demonstrate improvements in physical functioning in cancer cachexia, but evidence-based development is critical. For their use in clinical and regulatory decision making, studies demonstrating meaningfulness to patients as well as feasibility and validation are necessary.

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INTRODUCTION

Advances in diagnostic and treatment modalities have led to increased cancer survival rates and by 2030, it is estimated that the number of cancer survivors in the United States will reach 22 million.[1] As the number of people diagnosed with cancer continues to rise each year,[2] these developments in the fight against cancer are undoubtedly reasons to be hopeful, but they pose a new public health challenge: adequately treating and caring for those living with and through cancer. In addition to the disease itself, the intense anticancer therapies used to fight the disease can significantly affect health-related quality of life (HRQoL), particularly for those with advanced cancers.[3,4] For example, one of the most debilitating conditions in cancer is cachexia, a multifactorial muscle-wasting syndrome characterized by loss of muscle mass, weight loss, and fatigue.[5] Occurring in up to 80% of patients with advanced cancer,[6-10] it poses higher risks for the elderly and for those receiving chemotherapy.[8,11-15] Cachexia significantly decreases cancer survival[8,16-19] and progressively impairs patient's physical function—the ability to carry out day-to-day activities[20]—an important domain of HRQoL in cancer[8,14,21-23] and an important aspect of health for patients.[24-26]

Despite the severe impacts of cachexia on patient's survival and everyday functioning, there are currently no approved drugs in the United States for its treatment.[13] Although ongoing trials have shown some effect of anticachexia medicines on lean body mass, they have not been shown any

effect on physical functioning.[27-29] The failures in drug trials, especially because of the physical function end point, can in part be attributed to a lack of measures that capture meaningful information from patients. Regulators and researchers are aligned on the importance of capturing meaningful information by measuring what matters to patients in their day-to-day functioning in their journey of living with cancer.[30-33] In recent years, there has been a growing interest in using digital health technologies (DHTs) to capture patient-centric outcomes, importantly in the real-world setting, for valuable insights into how patients experience their disease.[34-39] Real-world applications of DHTs provide new opportunities for developing novel digital measures[40-42] of physical function in cancer cachexia. With DHTs, components of physical function can be captured as physical behavior[43,44] (eg, gait, mobility, overall physical activity, moderate-to-vigorous physical activity [MVPA], and sedentary behavior), and have been explored in patients with cancer to help shape interventions alongside other established assessments for a holistic capture of everyday functioning.[37,45]

In this narrative review, we summarize the subjective and objective assessments of physical function currently used in cancer cachexia clinical research. We outline gaps in current assessment modalities and discuss the path forward in using DHTs to capture real-world physical behavior as a measure of physical function. We also highlight recent developments in the digital health community in regard to the use of digital measures and discuss the fundamental need of establishing digital measures that matter to patients to advance the development of new therapies.

EXISTING METHODS TO ASSESS PHYSICAL FUNCTION IN CANCER CACHEXIA

Cancer cachexia is diagnosed by evaluating anorexia or reduced food intake, catabolic drive, lean body mass, muscle mass and strength, physical function, and various psychosocial effects.[5] In cancer cachexia clinical trials, regulators recommend assessing change in muscle mass and associated functional impairment as coprimary end points.[30] However, while muscle mass is often measured, physical function is neglected in this population. The three most common end points in cachexia trials are body weight or body mass index, global HRQoL, and lean body mass, and less commonly physical function, and other outcomes such as treatment toxicity, nutritional status, and symptoms.[46]

Despite its importance on long-term outcomes, meaningfulness for patients[24-26] and significant impact on HRQoL in cancer cachexia,[47] physical function has only been assessed in 35% of cancer cachexia trials.[46] Through direct patient input from available patient-focused drug development (PFDD) reports,[24] multistakeholder convenings,[25,48] and qualitative research, it is clear that patients with cancer cachexia care about improving physical function.[49-52] They want treatment options to consider meaningful factors that affect their physical and psychological well-being such as activities of daily living, including walking, climbing stairs, day-to-day tasks, maintaining energy, independence and caring for oneself, and being able to tolerate as well as adhere to cancer treatment.[26,48,49] This is critical, since therapeutics under development have yet to be proven effective in improving physical functioning.[30,53] This illustrates an important gap in the treatment of cancer cachexia and highlights the need for accurate and reliable assessments of physical functioning in cancer cachexia trials.

Commonly, physical function is measured with subjective clinician-reported outcomes (ClinROs), patient-reported outcomes (PROs), and objective in-clinic performance outcomes (PerfOs).[5] Although widely accepted and validated, these measures have limitations that are worth discussing as digital assessments methods enter the field.

ClinROs

ClinROs are based on clinician observation of the patient's health condition.[54] Widely accepted methods such as the Eastern Cooperative Oncology Group Performance Status Scale (ECOG-PS)[55] and the Karnofsky performance status (KPS)[56] are validated measures of a patients functional status in cancer.[57] These are shown to be predictive of survival and treatment outcomes in cancer, but are limited by clinician biases, interobserver variability, and inaccurate leveling of performance status because of low sensitivity.[58] They are only assessed episodically in laboratory or clinic settings, limiting their ability to detect subtle clinical change over time and capture a true picture of the physical behavior in the real-world.

PROs

PROs are reliant on direct patient report,[54] to capture multidomain HRQoL, patient's well-being, disease-related symptoms, treatment side effects, and physical functioning.[59] The most commonly used PROs in cancer cachexia are European Organisation for Research and Treatment of Cancer QoL Questionnaire C30 (EORTC-QLQ-C30), which consists of physical, social, cognitive, and emotional functioning subscales,[5,47,60] and Functional Assessment Anorexia/Cachexia Therapy (FAACT), which is an only cachexia-specific instrument.[46,47,61] Table 1 showcases their use in various clinical trials.

The EORTC-QLQ is a validated tool with sensitivity to change[74] with limited content validity (in cancer cachexia population for the intended use),[75] which is important to consider since concepts of physical performance are subjective and differ based on the disease as well as the severity of the disease.[74] The FACCT is also used in cancer cachexia trials.[28,63] The validated FAACT/Anorexia Cachexia Symptoms subscale assessing symptoms in cachexia[76] is used, more recently, as the primary composite HRQoL end point alongside body mass in an ongoing clinical trial

TABLE 1. Summary of Tools for Assessing Physical Function in Cancer Cachexia

Type of Outcome	Assessment Method	Benefits	Limitations	From Clinical Trials
Clinician-reported outcomes	KPS	Well-accepted, standard, validated, and low-cost tools in oncology	Subjective, potential to clinician biases, performed in clinic under supervision, episodic in nature	Significant improvement ($P < .05$) compared with placebo in anamorelin phase II[62]
	ECOG-PS			No significant improvement compared with placebo in enobosarm phase IIb (ClinicalTrials.gov identifier: NCT00467844)[63] Significant improvement ($P < .0001$) in a multidrug combination trial compared with baseline[64] Significant improvement within group compared with baseline ($P < .05$) but not significant when compared between arms in a multidrug combination trial[65] No significant improvement in either arm (single *v* multiple regimen) in a multidrug combination trial[66]
Patient-reported outcomes	FAACT	Validated multidomain cachexia-specific tool with physical functioning and symptom subscales	Subjective, potential to recall biases, ceiling effects, limited associations to objective measures, episodic in nature, burdensome for patients	No significant improvement in enobosarm phase IIb (ClinicalTrials.gov identifier: NCT00467844)[63]
	EORTC-QLQ	Validated multidomain HRQoL tools to capture physical, social, cognitive, emotional well-being, widely used to capture PROs in oncology		Significant improvement in multidrug combination trials when compared with single-drug regimen[67,68] Significant improvement in single and multiple regimen administration when compared with baseline ($P < .001$) but no significant differences between arms in a multidrug combination trial[66] No significant improvement in other multidrug combination trials[64,65] and multimodal intervention trial (ClinicalTrials.gov identifier: NCT01540968)[69]
Objective in-clinic performance outcomes	HGS	Simple, reliable, and acceptable assessments in that they imitate activities that patients would perform in their daily life Widely used validated assessments in cancer (6MWT), some (stair climb power) have high sensitivity and specificity in cancer cachexia, and others (HGS) are appropriate for patients who are frail and elderly[5,70]	Relevance and meaningfulness unclear as a measure of physical function, episodic in nature, requires in-clinic supervision, limited ecological validity as may not be a true measure of the free-living physical behavior, have possible floor effects in frail and elderly, burdensome for patients	No significant improvement in enobosarm phase IIb (ClinicalTrials.gov identifier: NCT00467844),[63] anamorelin phase II,[62] and anamorelin phase III (ClinicalTrials.gov identifiers: NCT01387269 and NCT01387282)[28]
	Muscle strength (knee flexors, knee extensors, or quadriceps)			No significant improvement in a multimodal intervention trial (ClinicalTrials.gov identifier: NCT01540968)[69]
	Timed-up-and-go, sit-to-stand			No significant improvement in multimodal interventions trial (ClinicalTrials.gov identifier: NCT01540968)[69]
	Stair climb power			Significant improvement ($P < 00.1$) compared with placebo in enobosarm phase IIb (ClinicalTrials.gov identifier: NCT00467844)[63]
	6MWT			No significant improvement in enobosarm phase IIb (ClinicalTrials.gov identifier: NCT00467844)[63] and anamorelin phase II,[71] and multimodal interventions trials (ClinicalTrials.gov identifiers: NCT01419145 and NCT01540968)[69,72] Significant improvement within group when compared with baseline ($P < .05$) but not significantly different between arms in a multidrug combination trial[65]
	SPPB (30-second chair stand test, or 10-minute walk speed test)			Ongoing multimodal intervention trial[73]

(continued on following page)

TABLE 1. Summary of Tools for Assessing Physical Function in Cancer Cachexia (continued)

Type of Outcome	Assessment Method	Benefits	Limitations	From Clinical Trials
Digital measures of real-world physical behavior measured by DHTs	Physical activity measured by SenseWear armband; activPAL	Potential to capture real-world physical behavior, provide continuous data points, less burdensome to patients, useful in exercise interventions as well as in capturing treatment effects	There is heterogeneity in measures derived from several types of sensors, and limited validation in this context to inform fit for purpose	Significant improvement ($P < .05$) in a combination regimen compared with single regimen in a multidrug combination trial[64] No significant improvement in either arm (single *v* multiple regimen) in a multidrug combination trial,[65] and in a multimodal interventions trial (ClinicalTrials.gov identifier: NCT01419145)[72]
	Step count, time standing, time stepping, and sedentary time measured by activPAL			Ongoing drug trial (ClinicalTrials.gov identifier: NCT01433263)
	Real-world gait speed measured by remote digital wearable sensors (not specified)			Unpublished drug trial (ClinicalTrials.gov identifier: NCT05546476)

NOTE. Multidrug combination trials include combination of various drugs in different arms. Multimodal intervention trials include nutrition, exercise, and anti-inflammatory medicines. Clinicaltrials.gov identifiers are provided when available. SenseWear Armband and activPAL are wearable sensors, a class of DHTs, that collect physical behavior and activity-related data in the free-living environment.

Abbreviations: 6MWT, 6-minute walk test; DHTs, digital health technologies; ECOG-PS, Eastern Cooperative Oncology Group Performance Status Scale; EORTC-QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FAACT, Functional Assessment Anorexia/Cachexia Therapy; HGS, hand grip strength; HRQoL, health-related quality of life; KPS, Karnofsky Performance Status; PROs, patient-reported outcomes; PS, performance status; SPPB, short physical performance battery.

(ClinicalTrials.gov identifier: NCT03743064). However, most cancer cachexia trials with published data measure HRQoL as a secondary end point and when measured, physical function is captured by PerfOs.

Even as patient-centered assessments, self-reported measures of physical function can be limited because of their subjectivity, episodic nature, high ceiling effects, and recall bias.[77] There is mixed evidence of associations between PROs and objective measures of physical function in cancer—some studies reported strong associations,[78,79] whereas others reported modest[80] to no associations.[81,82] This may be in part because of the nature of the PROs that are focused on global well-being that do not capture functional independence or real-world behavior of individuals, although they are important to patients. This supports the idea that PROs may need to be complemented by objective measures to provide a holistic picture of physical function, with a low burden on patients.[81,82]

PerfOs

PerfOs reflect performance fitness or strength-related tasks on the basis of supervised instructions often conducted in a controlled environment.[54] PerfOs that are common endpoints in cancer cachexia trials include hand grip strength (HGS), short physical performance battery (SPPB), timed-up-and-go, stair climb power, and 6-minute walk test (6MWT).[46,83,84] The HGS is highly feasible in older and frail patients, but its relevance as a measure of physical function is unclear.[5,70] It does not predict overall survival[85] and has inconsistent associations with low muscle mass in cancer cachexia.[23] The SPPB, a composite measure of balance test, chair stand test, and walking speed,[70] shows predictive value for functional decline[86] and mortality[87] in cancer. Similarly, the 6MWT, a validated measure of functional capacity in cancer,[88] also has predictive value for survival in cancer.[89,90] But in cancer cachexia, although performance on the 6MWT is associated with HRQoL,[91] it is not associated with improvement in muscle mass.[14] Other assessments such as the stair climb power are known to have better sensitivity and specificity in this population.[23] Overall, these are simple, reliable, and acceptable assessments in that they can imitate activities that patients would perform in their daily life, thus have utilities in measuring physical performances but not without limitations. Table 1 highlights their use in various clinical trials.

These in-clinic tests have been used inconsistently in trials and have several limitations related to lack of relevance to patients' everyday lived experiences or behaviors,[5] the episodic nature of assessment, burden on patients (for traveling to study sites and performing on the sites), requirement of the trained staff, and the possible floor effects and ceiling effects on he basis of the patients' ability.[70] They also tend to have modest association with subjective measures.[80,81] Still, the assessments have some value, just like the PROs or ClinROs, because patients care about being able to exercise and do weight-bearing activities in their daily life. Therefore, they may be best complemented by digital measures that capture real-world behavior with the help of DHTs.

Digital Measures of Real-World Physical Behavior

Real-world physical behavior, measured passively with DHTs as individuals go about their daily lives, is an additional assessment category of physical function beyond the perceived functional capacity reported by patients themselves, observed functional capacity reported by clinicians, and objective physical capacity assessed with in-clinic performance tests. This is an important distinction to make, since how individuals actually behave in their own real-world environment can be valuable to evaluating treatment safety, tolerability, and effectiveness.

Various components of physical behavior can be digitally measured such as physical activity, sedentary behavior, walking patterns and characteristics, and mobility.[31,35,37,39,78,92] Such measures are complementary to existing assessment modalities and consequently can be used to provide a more comprehensive understanding of physical functioning and a better basis for decision making in clinical development.

Wearable sensors are one class of DHTs that are frequently used in cancer cachexia observational research to measure real-world physical behavior.[28,35,72,93] Previously, the decline in physical function in relation to decreasing muscle mass was studied using in-clinic tests,[94] but the same association can be investigated now with accelerometers that provide objective and continuous insight into the physical behaviors of patients with cancer.[92,93] Wearable sensors with accelerometers are used to assess time spent in activities such as sitting, lying, standing, stepping, or sit-to-stand transitions in this population.[35] activPAL is an example of a thigh-worn accelerometer device with established feasibility and criterion-based validity in patients with cancer, as it accurately measures body positions and movements across functional levels (KPS scores).[36,82]

In cancer cachexia clinical trials, recently, measures derived from wearable sensors are used as end points, such as the physical activity assessed as primary efficacy end point alongside lean body mass in a multidrug combination trial,[65] as a secondary end point in another multidrug combination trial[64]; and step count and daily duration of activities assessed as exploratory end points in multimodal interventional trials,[72,95] as well as in unpublished phase II trials (ClinicalTrials.gov identifiers: NCT01433263 [96] and NCT05546476 [97]). As more trials adopt the use of DHT-measured outcomes of real-world physical behavior, there is opportunity for developing effective interventions that not only improve survival but also improve or preserve physical function.[31,35] Table 1 summarizes various assessment tools of physical functioning for clinROs, PROs, PerfOs, and digital measures that are used in cancer cachexia clinical trials thus far.

Cancer Cachexia Clinical Trials Show No Significant Changes in Physical Function Outcomes, Assessed Using the Current Methods

There is no approved treatment for cancer cachexia in the United States[13] and Europe,[98] while the only available treatment approved is in Japan.[29] There are trials that demonstrate improvements in lean body mass or body weight, but report no significant changes in measures of physical function.[53] As detailed in Table 1, anamorelin did not improve HGS (in phase III ROMANA trials)[28] or 6MWT (in phase II Japanese trial).[71] Enobosarm showed significant changes in stair climb power, but did not improve HGS nor 6MWT (in phase IIb trial)[63]; results of phase III (POWER trial) are yet to be published.[99] Trials that use real-world digital assessments are also shown in Table 1, but they are either ongoing or unpublished trials. Multimodal and multidrug trials with digitally measured physical activity outcomes also show inconsistent results. Here, it is important to note that some trials listed in Table 1 for combination therapies[64,67] and multimodal therapies[12,100] also show potential benefits in patient outcomes in this population, but multidrug treatments were not more effective than single-drug administration,[66] standard multidrug regimen does not exist yet, and the efficacy of multimodal interventions is not yet known.[101] Furthermore, multiple assessments, interventions, and regimens can be burdensome for patients in treatment.

Taken together, physical function improvement is a major gap and opportunity in cancer cachexia trials. One potential reason for the lack of effects on physical function is that current methods to assess physical function are inadequate. Established assessments of physical function are limited by clinician and patient bias, episodic measurement, recall and ceiling effects, and poor ecological validity. To better capture changes in physical function and facilitate discovery of potentially effective therapies, there is a need to develop better methods of assessing physical function in the real-world in a way that captures patients' lived experience and reflects aspects of physical function that matter to patients. Novel digital measures and assessment tools may provide a solution, but it is important to first understand what measures matter to patients.

PATH FORWARD WITH DIGITAL MEASURES OF REAL-WORLD PHYSICAL BEHAVIOR

With advances in DHTs, the landscape of clinical research is changing. DHTs can capture patients' health and well-being in the clinic and in the real-world to provide a more complete picture of their health status.[102] DHTs' applications are not limited to electronic assessments of PROs and digital assessment of in-clinic performance tests, as advanced technologies are now able to provide information about individual health behavior in the free-living environment.

DHTs such as wearable devices consisting of multiple sensor integration can now seamlessly gather multiple components of health and behavior; for example, a single device can have accelerometers, global positioning system trackers, and photoplethysmography sensors to assess components of physical activity and sleep patterns, life-space mobility, and continuous heart rate, respectively. Table 2 showcases some of their uses in clinical research in multiple therapeutic areas.

These types of DHTs play a pivotal role in oncology by evaluating diverse health information beyond physical activity or behavior.[110] Although their use is advancing, there is still untapped potential in optimizing cancer research, treatment, and care.[38] Thus far, DHTs have demonstrated feasibility and acceptability for monitoring patients with cancer during treatment.[37,39,111,112] and have been used in assessing treatment effects and benefits.[113] As such, DHTs hold promise in patient-centered drug development, particularly in studying the impact of treatments on physical function, a primary focus in drug trials and multimodal interventional trials for cachexia.

Recent Developments in Digital Measures of Real-World Physical Behavior

Digital measures of real-world physical behavior derived from wearable sensors are now slowly gaining traction in regulatory decision making. Some common digital measures used in clinical trials are presented in Table 2. They include digitally measured gait speed, step count, and time spent in MVPA. Specific wearable-derived measures such as stride velocity 95th centile (SV95C)[103] and real-world gait speed[105] have been qualified or are undergoing qualification through US Food and Drug Administration (FDA) and European Medicines Agency regulatory process. SV95C is a measure of peak performance in Duchenne muscular dystrophy, where speed of the fastest strides is recorded with high sensitivity to change.[103] Gait speed is a measure of speed of walking, and can be used to detect gait speed declines that are common in elderly or frail population with health conditions such as sarcopenia, multiple sclerosis, and others that affect motor function and mobility.[105]

As a measure of patient's physical function, real-world gait speed has potential in cancer cachexia as it provides a continuous evaluation of walking pattern and behavior.[114] Gait speed, measured in clinic, accurately predicts physical decline in elderly and frail individuals,[115,116] including in patients with cancer.[117] This is also evident in advanced cancer, where in-clinic gait speed is associated with muscle mass, HRQoL, and performance on the 6MWT, sit-to-stand test, and HGS.[118] This association with physical decline and with muscle mass and HGS can be studied using a wearable-measured real-world gait speed, which is less burdensome to the patients and provide more than just a snapshot of their physical capacity.[114] Furthermore, there is scientific rationale to measure gait speed in the real world, as gait speed measured in the laboratory is significantly lower than when measured in the real world.[119]

TABLE 2. Examples of Digital Measures of Real-World Physical Behavior Used in Various Therapeutic Areas

Digital Measure Real-World Physical Behavior	Therapeutic Area	Clinical Trial	DHTs Used	Regulatory Qualification Status
Daily motor activity, SV95C[103]	DMD	Phase II and III. Secondary end point. ClinicalTrials.gov identifier: NCT03039686	ActiMyo device to capture daily movement and activity levels; consists of two sensors worn on each ankle	Record of FDA COA LOI acceptance (DDT-COA-000103) Record of EMA qualification[104]
Real-world gait speed[105]	Sarcopenia in hip fracture and MS	Phase II. Exploratory. sarcopenia: ClinicalTrials.gov identifier: NCT02333331 Hip fracture surgery: ClinicalTrials.gov identifier: NCT02152761	Actibelt device to capture physical activity, consists of accelerometer, wearable in a belt buckle	Record of FDA COA LOI acceptance in sarcopenia (DDT-COA-000105) and MS (DDT-COA-000106) Record of EMA submission in sarcopenia and MS
Physical activity	Musculoskeletal pain in knee osteoarthritis	Phase II. Secondary end point. ClinicalTrials.gov identifier: NCT05025787	Actigraphy device, not specified	Record of FDA COA LOI acceptance (DDT-COA-000102)
Physical activity	Cardiology, chronic heart failure	Phase III. Secondary end point. ClinicalTrials.gov identifier: NCT03877237	Wearable activity monitor, not specified	Record of FDA COA LOI acceptance (DDT-COA-000114)
MVPA	Idiopathic pulmonary fibrosis; pulmonary hypertension	Phase III. Primary end point. ClinicalTrials.gov identifier: NCT03267108 Phase IV. Secondary end point. ClinicalTrials.gov identifier: NCT03717012	Actigraphy device, not specified Wearable activity monitor, MoveMonitor DynaPort	No record of digital measure COA qualification effort till date FDA-approved primary end point for the study of inhaled nitric oxide in hypertension associated with interstitial lung disease[106]
PRO-active[a] composite measure[107]	COPD	Phase III. Secondary end point. ClinicalTrials.gov identifier: NCT02085161	Wearable activity monitor, MoveMonitor DynaPort	Record of EMA qualification[108]
Step count and MVPA	Asthma	Phase IV. Secondary end point. ClinicalTrials.gov identifier: NCT04203797	Accelerometry device, not specified	No record of digital measure COA qualification effort till date
Physical activity	Cancer cachexia in (advanced stage NSCLC, pancreatic cancer)	Phase II. Secondary end point. ClinicalTrials.gov identifier: NCT01433263 [96]	activPAL	No record of digital measure COA qualification effort till date
Physical activity (sedentary, light and moderate) and real-world gait speed	Cancer, cachexia, (NSCLC, pancreatic cancer, colorectal cancer)	Phase II. Secondary end point. ClinicalTrials.gov identifier: NCT05546476 [97]	Remote digital sensors, not specified	No record of digital measure COA qualification effort till date

NOTE. Record of FDA COA LOI submission was searched on the FDA Drug Development Tool Qualification Project Search website: US FDA.[109]

Abbreviations: COA, clinical outcome assessment; COPD, chronic obstructive pulmonary disorder; DDT, drug development tool; DHTs, digital health technologies; DMD, Duchenne muscular dystrophy; EMA, European Medicines Agency; FDA, US Food and Drug Administration; LOI, letter of intent; MS, multiple sclerosis; MVPA, moderate-to-vigorous physical activity; NSCLC, non–small-cell lung cancer; PRO, patient-reported outcome; SV95C, stride velocity 95th centile.

[a]PRO-active composite measure is a measure of daily and clinical physical activity in a hybrid instrument of a PRO and accelerometer-derived data.

However, although there are numerous ways of measuring physical behavior, it is not well known whether any particular measure of physical behavior is more meaningful than others for individuals living with cancer cachexia. Real-world gait speed has already been incorporated in an ongoing cancer cachexia trial as a secondary outcome measure (unpublished; ClinicalTrials.gov identifier: NCT05546476),[97] and results of this trial and future trials, as well as qualitative evidence of meaningfulness to patients, will inform whether there is clinical utility as an outcome measure. Nevertheless, the utilization in various clinical trials (Table 2) showcases the feasibility of these assessment methods; further regulatory qualification would facilitate their use as primary or secondary outcomes and guide the approval of new drugs.[40]

Qualification of Digital Measures for Use in Drug Development

Qualification of digital measures as drug development tools (such as clinical outcome assessment or biomarker) is necessary and it is recommended by the FDA in their PFDD guidelines.[120,121] The digital health community has proposed mechanisms and frameworks for the qualification process.[40,122,123] This process entails first understanding what is meaningful to patients to measure and improve, generating evidence on its feasibility in this population, and subsequently establishing analytical and clinical validity of the measures.[40]

The first step is establishing that the measures being developed are meaningful for patients. The measures that matter framework[41] provides guidance on selecting assessment tools in a way that the measure of success of therapies is based on meaningful change to the patients. Additionally, rigorous methods are established for including the patient experience in clinical decision making,[121,124] and regulatory decision making,[34] which recommend gathering direct patient input on what matters to them in their disease experience and what improvement means to them, so that the therapies developed by evaluating these as outcome measures are more likely to improve the aspects of health that matter the most to patients. This process of cocreation ensures that the generated evidence is rooted in mutual value for all stakeholders, not just drug developers.[125,126]

The second step, developing and evaluating digital measures with the V3 framework for verification and analytical and clinical validation, is crucial to determine their utility in clinical trials.[42,75] Verification ensures that the sensor technology is appropriate for collecting data and depicting output as its designed to do.[42] Validation work demonstrates that the intended measure and the relevant clinical concept are accurately measured.[75] These processes help establish that intended digital measures are fit for purpose.

In clinical validation, the adequacy of the digital measures of real-world physical behavior in cancer is explored through their association with the standard performance scales, self-reported measures, as well as survival and treatment outcomes.[127] For example, in cancer, evidence suggests that digitally measured physical behavior (such as daily step count, sitting/lying, and time standing) is strongly correlated with the KPS and ECOG-PS, moderately correlated with PROs, and associated with survival, treatment outcomes, and treatment effects.[74,92,127] Furthermore, the measures of real-world physical behavior have applications in studying the effect of exercise interventions in cancer cachexia.[95,118] These considerations are critical and warrant further research as digital measures become incorporated in clinical trials, especially because there is heterogeneity in available wearable sensors and the measures of physical behavior used in cancer trials.[37]

Therefore, the foundational work necessary for moving forward is to generate evidence through qualitative research on the specific aspects of physical function that are important for patients with cancer cachexia to improve in treatment. The evidence then can help develop, validate, and qualify novel digital measures for clinical trials. However, qualification is a lengthy and costly process that requires alignment and input from stakeholders such as patients, clinicians/researchers, and regulators.

In conclusion, cancer cachexia is a complex metabolic syndrome that affects 80% of patients with advanced cancer and is characterized by muscle wasting, weight loss, and fatigue. Cancer cachexia has major effects on cancer survivorship and HRQoL, specifically physical functioning. Despite its burden on patients, there are no drugs approved to treat cancer cachexia in the United States. Existing qualitative evidence suggests that patients with cancer cachexia want to improve their physical functioning, especially their ability to independently exercise and perform activities of daily living. Clinical trials have failed to show improvement in physical functioning, which underscores the unmet need for meaningful assessment tools to measure physical function in cancer cachexia trials. Existing assessment tools to assess physical function are episodic in nature, burdensome to patients, and often lack ecological validity. Wearable sensors offer the possibility to address these limitations through passive, continuous, and remote assessment of patients' physical behavior. The important next steps lie in developing and validating digital measures of health and qualifying them for use in clinical development and regulatory decision making. By rooting this work in the patients' experience, with their participation throughout the process, we can ensure that the development of new therapies is based on, and stimulated by, evidence that creates value for all stakeholders.

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