Ametris

Digital Endpoint
Resource Guide

THERAPEUTIC AREA GUIDE

Oncology

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Oncology

Oncology remains one of the most challenging and complex therapeutic areas and continues to be the top priority for research and development in both private and public sectors. Billions of dollars are invested to understand how to deliver the right treatment to the right patient at the right time. Beyond innovations in therapeutics development, real time and actionable insights into patients' journey are critically needed for tailored cancer care. Digital health technologies (DHTs) such as wearables provide continuous data reflecting patients' function and physiology and could pave the way to optimize the efficacy and safety profile in a personalized manner.

An important aspect of cancer care is the quality of life before, during and after treatment.[1] The FDA and the EMA have taken notice and highlight the need for clinical trials to not only include survival and tumor-centric endpoints, but also those demonstrating a clinical benefit including physical function, quality of life, and symptom improvement.[2,3] Traditionally, conventional endpoints require long follow-up and large sample sizes (i.e., mortality), in-clinic visits (i.e., radiological tests; polysomnography), or are restricted to subjective self-report (i.e., European Organisation for the Research and Treatment of Cancer, Quality of Life Questionnaire (QLQ) 30; Pittsburgh Sleep Quality Index). Wearables and sensor-based DHTs provide these patient-centered outcomes continuously and remotely, reducing the burden of trial participation, increasing the probability of trial success, and improving management of the conditions.[4]

> *Another major consideration for oncology care is the management of adverse effects such as sepsis and cytokine release syndromes, some of which require inpatient care. Wearable devices can enable outpatient management by remotely monitoring vital signs such as heart rate, heart rate variability, oxygen saturation and temperature with AI-driven early detection, substantially broadening the access to life saving therapies.*

Opportunities with Wearable-Based Digital Endpoints

- Direct measures of real-world function
- Accelerate clinical development timeline
- Demonstrate patient-centric benefits
- Complement PRO-based evidence
- Continuous, rich data sets
- Objective measures and quantifiable changes in participant function
- Low Burden, remote data collection
- Future-Proof Raw Data

Selected Digital Endpoints for Oncology

CONCEPT	ENDPOINT	DEFINITION
Physical Activity	Moderate to Vigorous Physical Activity (MVPA)	Time spent in moderate and vigorous activity (Energy expenditure of > 3 METs) while awake[5]
	Non-Sedentary Time	Time spent in non-sedentary behaviors (energy expenditure of > 1.5 METs) while awake[5]
	Daily Total Activity Counts	The total number of counts on the x, y, and z axes
	Walking (step count, peak cadence, walking speed)	Total counts of steps taken per day; number of step per min; walking speed
Sleep	Total Sleep Time (TST)	Total amount of time spent asleep during sleep period[6]
	Wake After Sleep Onset (WASO)	Amount of time spent awake during sleep period[6]
	Sleep Onset Latency (SOL)	Amount of time it takes to fall asleep[6]
	Sleep Efficiency (SE)	Percentage of time spent asleep during time in bed[6]
Cardinal Symptoms *Cough*	Cough Frequency	Number of cough events during a designated time
	Cough Bouts	Bout length, bout duration, hours with highest bout density, and/or periods without bouts

Selected Digital Endpoints for Oncology

CONCEPT	ENDPOINT	DEFINITION
Vital Signs	Heart Rate (HR)	The number of heart beats per minute
	Respiratory Rate (RR)	The number of breaths per minute
	Atrial fibrillation (Afib)	Occurrence of abnormal heart rhythm (arrhythmia)
	Oxygen Saturation	The fraction of oxygen-saturated hemoglobin relative to total hemoglobin in the blood
	Blood Pressure	Systolic blood pressure measures the force the heart exerts on the walls of the arteries each time it beats. Diastolic blood pressure measures the force the heart exerts on the walls of the arteries in between beats.
	Skin Temperature	Absolute temperature measured from the skin in contact with the wearable base

Physical Activity

People with cancer find physical functioning to be beneficial for overall well-being; in fact, physical activity lessens treatment-related side effects, reduces recurrence and mortality, and correlates with quality of life.[7,8] Yet traditional, self-reported data gathering is prone to bias, with persons tending to over-report their activity. Wearable devices can objectively qualify the activity intensity and its relationship with health outcomes, overcoming the subjective bias related to self-reporting. Moderate-to-vigorous physical activity (MVPA) quantified with a wearable detected differences at 3-and 6-months post intervention.[9] Step counts captured by a wrist-worn wearable correlates with higher quality of life, physical functioning, role functioning, and emotional functioning, plus lower dyspnea, pain, and depression scores.[10] A phase 2 trial investigating a novel treatment for patients with cancer cachexia reported data collected from wearable sensors demonstrated an average increase of 72 minutes per day of non-sedentary physical activity in the treatment group compared to controls, providing an objective, measurable benefit in this multifaced condition.[11]

Sleep

Getting a good night's sleep is a challenge for up to 50% of cancer patients,[12] in part because of the side effects of their treatment. However, sponsors have traditionally lacked simple, validated ways to gather real-time quantitative sleep data. Dedicated sleep labs are expensive, and patient-reported outcomes are subjective and subject to recall bias.[13] In contrast, digital health technologies provide affordable, daily, and objective assessments of how people sleep at home. Multiple studies have used wearables to objectively measure sleep and assess its impact on people with cancer. An analysis of seven such studies linked sleep problems before or during cancer therapy to poorer response to treatment, shorter time to progression, and reduced overall survival.[14] Wearable quantified poor sleep efficiency (SE) and greater wake after sleep onset (WASO) predicted increased mortality in women with breast cancer.[15]

Cardinal Symptoms *Cough*

Cough is a significant yet often under-researched and under-treated symptom in oncology. A review of studies investigating the cause of Drug-induced interstitial lung disease (DIILD) reported that cancer drugs were the leading cause in 23-51% of cases, and that mortality rates following DIILD diagnosis in oncology were higher - ranging from 14-51% compared to 0-41% in non-cancer setting.[16] Cough is a common symptom in patients with lung cancer, affecting 57% in a study of 223 outpatients, with half of those affected indicating that they felt their cough was severe enough to warrant treatment.[17] Patients with lung cancer report persistent cough as a significant symptom impacting their daily life.[18] The presence of cough is an early indicator of pneumonitis, a serious complication of radiotherapy (which is a common lung cancer treatment) and can be fatal if left untreated.[19] Continuous, objective cough monitoring with wearable sensors over weeks or even months following cancer treatment can provide a more accurate measure of cough compared to short-term monitoring and PRO data. Cough detection using digital data collected in a real-world environment was shown to have 90% sensitivity compared to ground truth.[20] Detection of cough using digital health monitoring solutions can help improve patient outcomes and provide more accurate and sensitive outcome measures to assess efficacy of cough treatments.

Use in Clinical Studies

A review of 25 cancer clinical trials found adherence ranged from 60% to 100%.[21] The studies asked participants to wear the digital health technologies for periods ranging from eight to 270 days to capture outcomes including physical activity, circadian rhythm, sleep, and skin temperature. A systematic review of 199 oncology research studies that included wearable devices found high adherence rates, with 73% of the studies citing adherence rates of 80% or greater.[22] This review supports that wearables provide clinically relevant metrics that are otherwise difficult to accurately capture (such as physical activity and sleep); more than 78% of studies reported statistically significant relationships between wearable measures and established clinical outcomes of interest.

Immunotherapy-Related Adverse Events

Novel treatments for cancer such as CAR-T cell and T-cell engaging immunotherapies have great potential to advance cancer care, but one major challenge is the risk of severe, life-threatening toxicities such as cytokine release syndrome (CRS), sepsis, and neurotoxicity.23 Timely response to events like CRS can mitigate worsening severity and costs and improve patient outcomes.24 Wearable devices offer the opportunity to more continuously monitor patients, enabling the earlier detection of these adverse events as well as gathering more standardized data to help better characterize these events and treatment response High-frequency and high-fidelity data gathering can facilitate the development of artificially intelligent algorithms that will aid in patient safety monitoring and allow for more outpatient care with extended geographies. For example, using data from a publicly available benchmark dataset that collected vital signs every hour, a model was developed to effectively predict sepsis before clinical onset.[25] A digital health solution for monitoring immunotherapy-related adverse events allows for reduced duration of hospital stays while maintaining patient safety, thereby reducing the cost and accelerating the development of life-saving immunotherapies.

Regulatory Guidance

GUIDANCE

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations: Final Guidance for Industry, Investigators, and Other Stakeholders (December 2023)[26]

KEY POINTS

- FDA provides recommendations on the use of digital health technologies (DHT) for clinical development
  - Defines DHT and offers guidance on the selection, verification, validation, use, and risks
  - Encourage sponsors to engage with DHT manufacturer in using DHTs in clinical trials

GUIDANCE

Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics: Guidance for the Industry (December 2018)[2]

KEY POINTS

- FDA provides recommendations for applicants on endpoints for cancer clinical trials.
  - States cancer drug approval should be based on direct evidence of clinical benefit
  - Lists quality of life and improved physical functioning as examples of clinical benefits

GUIDANCE

Guidance on the clinical evaluation of anticancer medicinal products: draft guideline (January 2019)[3]

KEY POINTS

- EMA provides guidance on all stages of oncology clinical drug development
  - Lists survival measures and patient-reported outcomes as possible primary endpoints
  - Notes that adverse drug reactions affect patient's quality of life

GUIDANCE

Characterizing, Collecting, and Reporting Immune-Mediated Adverse Reactions (imARs) in Cancer Immunotherapeutic Clinical Trials (October 2022)[27]

KEY POINTS

- FDA provides recommendations for data collected to assess imARs and to include in new drug application (NDA) or biologics license application (BLA) for cancer immunotherapy drugs
  - States sponsors should prospectively design protocol to capture information needed to evaluate a potential imAR
  - Notes that sponsors should discuss this plan with the clinical review division early in development

Regulatory Guidance

GUIDANCE

Core Patient-Reported Outcomes (PROs) in Cancer Clinical Trials (October 2024)[28]

KEY POINTS

- FDA provides recommendations for collection of PROs in cancer clinical trials
  - States that this guidance focuses on PROs, some recommendations may be relevant to other clinical outcome assessments, including performance outcomes
  - Identifies physical function as a core PRO category
  - Notes that methods to lessen patient burden should be explored, including assessments outside of the clinic

To learn more about how your clinical program can benefit from using digital endpoints,

please contact us to schedule a meeting with a member of our Science team.

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