

Cancer-Related Fatigue Outcome Measures in Integrative Oncology: Evidence for Practice and Research Recommendations

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ABSTRACT

Cancer-related fatigue (CRF) is one of the most common symptoms across the cancer continuum and is often underreported and undertreated. Defined as a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or its treatment, CRF includes physical, emotional, cognitive, and spiritual dimensions. Patient-reported outcome (PRO) measures are the most widely used tool to screen for and assess fatigue and the associated negative impacts on quality of life. However, selecting subjective CRF measures can be complex. This has resulted in the availability of and inconsistent use of numerous PROs, limiting the ability to cross-compare outcomes clinically and within research. To address this, the PROs that are most widely reported in the literature are recommended to support the standardization of a core set of validated measures. The National Comprehensive Cancer Network single-item tool for clinical significance is recommended for quick use in clinical environments; the Brief Fatigue Inventory allows for fast, easy, helpful cutoffs on severity threshold for triage, and measures both severity and interference with daily functioning; while the MD Anderson Symptom Inventory allows for multisymptomatic assessment. In addition, a fundamental consideration for any PRO use is the administrative burden on the patient and clinician. In this review, we aim to summarize current, validated PROs specific to CRF to aid clinicians and researchers in patient care and in study design and implementation. We conclude with suggestions for future directions in CRF research that can increase the possibility for long-term impact on future guidelines of fatigue management.

PERSPECTIVE

Lisa Sprod, PhD, MPH, provides perspective on [page 278](#)

Introduction

The National Comprehensive Cancer Network (NCCN) guidelines¹ define cancer-related fatigue (CRF) as “a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.” For patients undergoing treatment, different chemotherapy agents, surgery, and radiation can cause acute or persistent CRF that impacts how tolerable they find their therapy. CRF can be either short- or long-term, with as many as one-fourth to one-third of survivors experiencing CRF for up to 10 years after cancer treatment.² It is widely understood to be a multidimensional symptom assessed by clinicians and researchers for presence, severity, impact on quality of life (QOL), and interference in activities of daily living. Due to the subjective and multidimensional nature of CRF, researchers should measure CRF across the emotional, cognitive, physical, and spiritual³ domains. There is great diversity in the patient-reported outcomes (PROs) used to measure CRF throughout clinical practice and research. The numerous PROs available and their inconsistent use limit the ability to cross-compare outcomes clinically and within research. In particular, the

difficulty associated with the diversity of CRF measures can lead to challenges in comparing study results across populations of patients with cancer.

The Society of Integrative Oncology (SIO) is a nonprofit, multidisciplinary professional organization that promotes rigorous, evidence-based, comprehensive integrative approaches for patients with cancer and for survivors. As members of the SIO research committee, we seek to clarify CRF PROs for oncology clinicians and researchers. Therefore, in this whitepaper, we (1) define CRF and summarize CRF prevalence, impacts, and associations across the cancer continuum; (2) discuss the challenges for diagnosis and treatment, including potential mechanisms and interventions; (3) introduce CRF measurement issues; (4) summarize the CRF PRO measures most widely reported in the literature; and (5) provide recommendations to oncology clinicians and researchers on which validated CRF PRO measures to use. We will limit any discussion of objective measures to focus on recommendations for measuring patient-reported CRF. A previous whitepaper written by SIO Research Committee members on pain PROs with similar goals has been published.⁴

Prevalence

Cancer-related fatigue is among the most common symptoms across cancer types and is often underreported and undertreated. Patients across the cancer continuum—including those recently diagnosed or in treatment, as well as long-term survivors⁵—often report CRF as among their top 3 symptoms, describing it as the most distressing of all symptoms.⁶ CRF is present in 25% to 99% of patients who are undergoing cancer treatment² and in 19% to 82% of patients post treatment^{7,8}; the overall pooled prevalence is 52%.⁹

Studies reporting age associations with CRF have been inconsistent. For example, Al Maqbali et al¹⁰ report no

association between age and CRF, whereas Alvarez-Bustos et al¹¹ report younger people having higher levels of CRF. The latter finding is supported by a review of studies across the United States, United Kingdom, Norway, Canada, and Sweden, where 31% to 100% of adolescent and young adult (aged 13-24 years) survivors reported CRF¹² as a significant and disabling problem. However, this prevalence based on age should be considered with caution in consideration of the underrepresentation of older age groups in cancer clinical trials.^{13,14}

With respect to gender, recent meta-analyses report female patients having a higher prevalence of and risk for CRF.^{9,10} Prevalence can further be broken down by cancer type. An epidemiological study using multidimensional CRF measures (n = 2244) reported that patients with breast cancer had the lowest adjusted mean physical fatigue values. In contrast, those values were markedly higher in those with stomach, lung, kidney, pancreas, and endometrium cancers.² These prevalence reports indicate variability in CRF across cancer types, and that females report CRF in higher numbers.

Negative Impacts and Associations With CRF

Those with CRF often experience reduced QOL.¹⁵ Persistent CRF limits the ability to work, complete activities of daily living, and maintain social relationships.¹⁶ Tasks such as household chores, running errands, and meeting the needs of family members can become exhausting. This results in a loss of interest in individuals' usual activities and in reduced concentration and memory/recall.¹⁷

CRF is a comorbid symptom with other ailments including pain, sleep disturbance, anemia, cachexia, sarcopenia, mood disorders, spiritual concerns, anorexia, and various gastrointestinal symptoms (eg, mouth sores, xerostomia, abdominal pain) leading to loss of appetite.¹⁸⁻²⁰ As a result, measuring CRF

as an individual symptom isolated from its related conditions becomes complicated.^{21,22} This is particularly challenging in relation to depression as it is difficult to find fatigue and depression scales that do not contain similar concepts. For example, the Patient Health Questionnaire-9, a commonly used depression scale, has a question—"Feeling tired or having little energy"—that directly overlaps with fatigue. It also contains questions that would be expected to be impacted by either depression or fatigue, such as, "Trouble concentrating on things such as..." Across CRF dimensions, there is an inverse association between CRF and psychological resilience, which has a direct impact on improvement in QOL. This has been observed in studies²³ using Antonovsky's Sense of Coherence (SOC) scale, where resilience has a mitigating effect on the development of fatigue. SOC is directly linked to the concept of salutogenesis, which focuses on how people use coping mechanisms to maintain their health despite stressful life situations.²⁴

Challenges for Diagnosis and Treatment

Diagnosing CRF is challenging due to the condition's multifactorial quality, which may be further complicated by how clinicians measure and assess CRF. Researchers recommend that diagnosis be informed by 4 criteria: (1) Indicators of symptom presence should be persistent for 2 or more weeks; (2) there should be evidence of distress or impairment; (3) the distinction should be made that the condition is related to cancer or cancer treatment; and (4) there is absence of any previous or existing psychiatric disorder.^{21,25} This last criterion should be viewed with skepticism. This is because any preexisting or current psychiatric disorders do not rule out the development of CRF after a cancer diagnosis, in fact they can often overlap. These challenges lead to clinical guidelines calling for a differential diagnosis to rule out comorbidities, namely depression.²⁶

While the focus of this manuscript is not CRF treatment, it is worth noting the current research in this area. No treatment mode is known to be most effective for CRF in all cases; however, a meta-analysis of randomized control trials outlines 4 major types of CRF treatments that are recommended for adult patients with cancer: exercise; psychological intervention; exercise plus psychological intervention; and pharmaceutical intervention.²⁷ Interestingly, Mustian and colleagues²⁷ report that certain intervention modes may be more effective for treating CRF at different points in the cancer treatment trajectory. Overall, the findings of this study demonstrate the efficacy of exercise and psychological interventions for improving CRF during and after primary treatment. With respect to pharmacological treatments, Chow and colleagues²⁸ report findings from a systematic review and meta-analysis of 20 randomized control trials concluding

that methylphenidate, modafinil, and paroxetine were superior to placebo; methylphenidate and modafinil were equivalent to one another; and paroxetine was superior to both methylphenidate and modafinil. Chow et al also stated that more safety data are required for pharmacologic interventions. A systematic review²⁹ of randomized controlled trials on integrative therapy interventions with CRF as the primary outcome included 30 studies; the quality of trials ranged from 2 to 8, with a mean score of 5.3, with most scores between 5 and 7 (n = 20). The results indicate that cognitive behavioral therapy combined with hypnosis and American ginseng is likely to be effective in patients receiving cancer treatment. For those in the posttreatment population, acupuncture, mindfulness-based interventions, and qigong/Tai Chi Easy™ were all found to be likely effective in reducing CRF. Furthermore, additional studies have demonstrated promising

complementary and integrative interventions with positive results at different points across the cancer continuum, including yoga,^{30,31} acupuncture,³² art therapy,^{33,34} and mindfulness-based stress reduction.^{32,35} Such herbal medicines as *Paullinia cupana*,³⁶⁻³⁸ *Uncaria tomentosa*,³⁹ *Viscum album*,^{40,41} and American and Asian ginseng,^{42,43} as well as some prescribed in traditional Chinese medicine,⁴⁴ have evidence of safety and efficacy, although additional research with high-quality methodology is needed.

Additional insights have been gained through pragmatic research involving patients with CRF, assessing the entire integrative oncology approach. This research includes nonrandomized trials that are patient-preference controlled. Findings suggest that patient-tailored multimodality integrative oncology treatment, adapted to patients' particular preferences and QOL-related concerns, may also alleviate CRF.⁴⁵⁻⁴⁷

PERSPECTIVE BY

Lisa Sprod, PhD, MPH

Deciding Which Cancer-Related Fatigue Assessment Tool to Use Just Got Much Easier

Cancer-related fatigue (CRF) is most often evaluated using patient-reported tools, making it subjective in nature. In addition, CRF is multidimensional and often a comorbid condition occurring with mood disorders, pain, and sleep disturbance, among others. Numerous tools have been developed to assess CRF, yet it remains the most common and persistent symptom and/or adverse effect resulting from cancer and its treatment, often lasting many years. In a large multicenter study (n > 3000), Wang et al found that moderate to severe fatigue is common in cancer survivors during active treatment and beyond.¹ Other investigators have found that up to 99% of patients with cancer report CRF;

and in up to one-third of survivors, fatigue persisted for as long as 10 years after the end of therapy.²

Despite the high prevalence of CRF, it is still thought to be underreported and undertreated, perhaps in part due to confusion about how to best assess it. With so many survivors of cancer negatively affected by CRF, investigators have focused their efforts on attempting to determine the most effective ways to reduce its impact. Exercise, psychological interventions, and pharmacological treatments have proven to offer some improvement in CRF. As a coauthor on a meta-analysis conducted to determine which intervention was most effective of the 3 listed above, I examined the wide variety of tools used

Mechanisms of CRF

Because this paper focuses on the assessment of CRF, it is important to introduce the complex etiology of CRF that contributes to the challenges in its measurement. The etiology of CRF is not well understood, and this hinders progress in ways to diagnose it and in finding interventions that alleviate this persistent syndrome.⁴⁸ CRF mechanisms and the associated hypotheses are divided across the central and peripheral domains. Peripheral fatigue disrupts central stimulation and muscle response; it is characterized both by a lack of adenosine triphosphate, a compound that provides energy to drive processes such as muscle contraction, and by a buildup of metabolic by-products such as lactic acid. In contrast, central fatigue extends from the central nervous system (CNS), including the brain and spinal cord. It is associated with changes in the synaptic junctions, which impact the function of

neurotransmitters within the CNS. These synaptic junction changes further impact muscle function that are not explained by peripheral factors.

Central fatigue includes 5 distinct hypothesized mechanisms of action: (1) hypothalamic–pituitary–adrenal axis dysregulation, (2) circadian rhythm dysregulation, (3) serotonin dysregulation, (4) vagal afferent activities, and (5) neuroendocrine impairment.^{49–51} A growing interest in neuroimaging studies that focus on the disruption of brain connectivity and changes in brain metabolites may lead to a sixth hypothesis that goes beyond serotonin dysregulation.^{52,53} Three hypotheses about the potential mechanisms of peripheral fatigue are (1) degeneration of muscle function, (2) impaired adenosine triphosphate/contractile properties, and (3) impaired physical function.^{49–51} Cytokine dysregulation as a mechanism of action is hypothesized to affect both central and peripheral fatigue. To date, the

most studied aspect of etiology concerns the cytokine hypothesis, demonstrating activation of proinflammatory cytokines as a common factor that leads to CRF and other behavioral changes, known as “sickness behavior.”⁵⁴ One such study involved women undergoing chemotherapy for breast cancer to investigate the potential for predictors of fatigue in relation to cytokine levels.⁵⁵ Earlier studies demonstrate support for other hypotheses, such as between heart rate variability and CRF^{56,57} and between muscle contractile properties and CRF.⁵⁸

Measurement Concerns

Many factors influence the chosen CRF measurement, contributing to the lack of PRO consistency used across clinical practice and research. The varying nature of CRF is reflected in the diverse recall periods of different PROs (eg, in the last week; within the past 24 hours), varying state (eg, fatigue at its worst; on average; right

to assess CRF. As an investigator, I have spent countless hours deciding on the best tool to use in my research. Assessment tools vary in their length; the ideal time in which to use them; the recall period; the constructs evaluated; and their sensitivity, reliability, and validity. All of these considerations may leave investigators and clinicians unsure of the best tool for their particular need.

The authors of the accompanying article have done a phenomenal job providing information that will aid investigators and clinicians in determining the best tool for their needs.³ Specifically, the article provides information that may clarify the best tool for assessing CRF based on factors such as the reason for assessment of CRF (clinical or research) and patient and clinician burden. This article provides a thorough overview of CRF, including prevalence, potential mechanisms, and common comorbidities. Next, the authors describe the challenges associated with choosing the appropriate tool and considerations one should make. With that backdrop, clinicians and investigators are able to utilize the comprehensive tables provided by the authors that categorize tools based on use for screening (Table 1),

unidimensional measures (Table 2), or multidimensional measures (Table 3). Information on populations in which the tools have been validated, whether the tools have been translated and/or culturally adapted and validated, the number of items in each tool, the type of rating scales the tools use, the estimated completion time of the tools, and more is available. This article will be one I keep close at hand when reading articles that include CRF as an outcome, and I will certainly rely on it as I choose CRF measures in my research. In addition, this article may serve as a model that inspires investigators and clinicians to comprehensively review other outcomes with multiple tools for assessment.

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now), and severity (eg, none, mild, moderate, severe). Different PRO instruments measure different constructs that reflect fatigue's multifaceted nature, including its impact on physical function, mental focus and capacity, emotional state, and social interactions. Instruments that capture global fatigue symptoms may mask other symptoms and conditions. However, unidimensional measures⁵⁹ of CRF that are subscales of more extensive, multifactorial tools can be helpful for a brief screening assessment. The measurement issues that will be discussed in greater detail are subjectivity, the intended measurement purpose, psychometric properties, the timing of assessment, methodological considerations, and differences across languages.

Subjectivity

CRF is a subjective, multifactorial experience that varies in severity and duration; it also has alleviating and aggravating factors. This pervasive symptom has predominantly been measured based on patient reports. Clinicians and researchers assess these reports for many aspects, including presence, severity, and distress, as well as distinguishing among the physical, emotional, cognitive, and spiritual dimensions of CRF.

Intended measurement purpose

The intended purpose of an instrument is also essential to consider when selecting a CRF PRO measure. Research purposes may necessitate different measures than clinical purposes. In both settings, the burden of implementation must be considered. Data collection may be burdensome for both assessor and the patient, so measures that can be completed quickly with limited disruption of the clinical workflow and an easy interpretation are often preferred. Furthermore, some measures are appropriate for brief screening, while others are more suited to support a diagnosis, intervention, or health outcome assessment of CRF. The magnitude of patient-reported symptom burden is critical when a decision must

be made about which measures should be used to capture clinical meaningful symptom burden to determine CRF management. For example, the NCCN guidelines on CRF describe a 0-to-10 scale of fatigue severity and indicate that a score of 4 or greater, indicating moderate to severe fatigue severity, would call for CRF management in a clinical setting.¹ The simple "Fatigue worst" severity item can be found in several validated PRO assessment tools, including the Brief Fatigue Inventory (BFI) assessment tool,⁶⁰ the MD Anderson Symptom Inventory (MDASI) multiple symptom assessment tool,⁶¹ and the Edmonton Symptom Assessment System (ESAS-r), which is a widely used palliative care tool.⁶² Research from a multicenter study on the optimal threshold of fatigue severity category for clinically meaningful impact on functioning confirmed the NCCN guideline consensus, that a score of 4 or greater presents moderate fatigue and 7 or greater presents severe fatigue.⁶³ The clinical actionability of measurement results can often be unclear. The availability and cost of measures are an additional concern. Some are available for no-cost public use, while others require payment for licensing fees. Researchers should consider these crucial aspects when making decisions about which PRO to use in a study.

Psychometric properties

The available psychometric properties of reliability, validity, and sensitivity are important for making PRO use decisions. Establishing the validity of an instrument is an ongoing process, and studies assessing validity are integral to clarify the purposes and contexts in which PROs are suitable. It is also vital to understand that an instrument may not be valid across different settings or contexts. Examples of these purposes or contexts include predicting treatment outcomes in a particular type of cancer or treatment phase, discriminating between fatigue and depression, or using measures in specific populations. Where possible, it is advisable to compare

findings of different studies with similar contexts and populations to rule out any concern of a PRO being used due to popularity over performance.⁶⁴

Timing of assessment

Another measurement issue concerns the question of the timing of fatigue assessment, especially during the trajectory of disease or treatment directly impacting CRF severity. It is necessary to differentiate among clinical settings: sometimes, for instance, fatigue is relatively "stable" (eg, during survivorship), and at other times, fatigue "spikes" as a result of oncology treatment. This can happen following stem cell transplant, major surgery, or a chemotherapy protocol, such as when fatigue emerges in "pulses" that rise at chemo days 2 to 3 and improve toward days 7 to 10. In these cases, chemotherapy-related fatigue may drive cancer-related fatigue. When subjects are undergoing chemotherapy, the timing of the baseline and follow-up CRF and health-related QOL (HRQOL) assessments is critical. In those cases where chemotherapy toxicity is the main fatigue etiology, there is a need to establish "optimality of assessment"⁴⁵ to ensure that clinicians keep a similar time interval between the administration of chemotherapy (baseline) and the follow-up assessments. So, if an initial assessment was performed at chemotherapy day 3, the next assessment(s) should also be timed to day 3 of the next chemotherapy cycle(s). Provided that the chemotherapy regimen remains unchanged, clinicians could consider the assessment optimal if it took place within a similar interval between the administration of chemotherapy and the follow-up visit at baseline and the follow-up assessments.⁴⁵ Clinicians and researchers should carefully consider measurements that align with the timing of key aspects of the patient's experience. For example, it may be necessary to measure the development of CRF at cancer diagnosis before treatment and then throughout treatment (eg, weekly)

TABLE 1. Category 1 Validated Patient-Reported Cancer-Related Fatigue Assessment Instruments

Instrument name	Validated population	Translation and/or cultural adaptation validation	No. of items	Constructs measured	Response options; recall	Clinically relevant cutoffs	Estimated completion time	Practicalities
Single-item screening instrument exception								
MYCaW⁷³	Mixed cancer population	No data	2	Identify 2 significant concerns and score severity	7-point Likert scale ⁷⁴	0-5, of no concern; 6-10, of significant concern; written narrative	Baseline: 3-5 minutes; follow-up: 5-7 minutes	Nonprofits: no-cost license; for-profit: commercial license ⁷⁵
Category 1: Single-item screening instruments								
CS⁷⁶	Solid tumor, including lymphoma; any stage with ECOG score 0-3	No data	1	Severity	0-10 scale; 3-day recall	Score of 5	>2 minutes	No cost; paper-and-pencil or electronic
FT⁷⁷	AYA brain tumor survivors	No data	1	Level of fatigue	Vertical thermometer image: bottom end "no fatigue" (0); top end: "worst fatigue imaginable" (10); 7-day recall	0, no fatigue; 1-3, mild fatigue; 4-6, moderate fatigue; 7-10; severe fatigue	>2 minutes	No cost; paper-and-pencil or electronic
NCCN⁷⁸	All cancer population aged more than 12 years	No data	1	Clinically significant, presence or absence of fatigue	"How would you rate your fatigue on a scale of 0 to 10 over the past 7 days"; 0 = no fatigue; 10 = worst fatigue imaginable	Mild, 1-3; moderate, 4-6; severe, 7-10	>2 minutes	No cost; paper-and-pencil or electronic, face-to-face interviews, or telephone interviews
ZSDS⁷⁹	Ambulant oncology; receiving treatment for malignancy	Azerbaijani/Russian, ⁸⁰ Arabic ⁸¹	1	Clinically relevant	4-point Likert scale; 4 = most unfavorable response	<2	>2 minutes	No cost; paper-and-pencil

AYA, adolescent and young adult; CS, Clinical Significance; FT, Fatigue Thermometer; MYCaW, Measure Yourself Concerns and Wellbeing; NCCN, National Comprehensive Cancer Network; ZSDS, Zung Self-Rating Depression Scale.

or measure CRF after an intervention has been initiated to assess its efficacy. The latter assessment would need to be tailored depending on the therapy initiated.

Methodological considerations

Finally, Wang points out the methodological concerns associated with "response shift."⁵¹ This concept concerns the point at which patients experience fatigue such that it changes how they judge the severity or intensity of CRF. This response shift can lead to underreporting of CRF, because patients may adapt their internal standards, values, or lifestyles to their illness perception. As a result, tracking changes in CRF

over time can represent a response shift rather than a reduction of the symptom. Alternatively, it could represent a response (or lack thereof) to treatment. To differentiate between response shift and treatment response and address the potential for negating internal validity, Howard and colleagues⁶⁵ recommend extending the traditional pretest-posttest study design with a "thentest." In this scenario, respondents are asked to recall the point in time at which the pretest was administered, thereby giving a renewed judgment on their pretest levels. This method has been used to assess response shift in patients undergoing radiation for cancer who report CRF.⁶⁶

Language challenges

Before the NCCN guidelines for fatigue were established, research has demonstrated that patient language is a challenge for CRF measurement. Not everyone uses similar words to describe their CRF experiences,⁶⁷ and this creates further problems in diagnosing CRF's presence or severity. In other words, the distinctions that different people make among exhaustion, tiredness, weakness, fatigue, and lack of energy is unclear.⁴⁹ A study that sought to identify clinical associations of 3 fatigue word descriptors—"fatigue," "weakness," and "lack of energy"—found that these terms are not synonymous.⁶⁸ For

instance, studies of PRO measures have found that fatigue is only inherently understood in English and French⁶ and key fatigue terms (weakness, tired, energy) are understood and used differently across cultures, generations, and languages.^{69,70} In addition to differences across language, a study reported that more than half of the most commonly used cancer PROs do not meet plain-language best practices.⁷¹ Differences across language and low health literacy, coupled with the nonadherence to plain-language practices in PRO development, result in the risk of data loss. However, well-validated patient-report measures that are translated into diverse languages can be pooled to analyze the data from multinational clinical research and provide reliable symptom assessment.⁷² Increasingly, comparable fatigue PRO data support a standardized use of well-defined terminology based on professional consensus and guidelines.

Fatigue PROs

While instruments to evaluate CRF PROs are numerous, we summarize selected measures most widely reported in the literature. **Tables 1-3**⁷³⁻¹⁴⁴ outline the contexts in which researchers have tested these measures for reliability and the types of validity assessed. We excluded measures that were missing information for 2 or more of the categorical properties included within **Tables 1, 2, and 3**. These categories comprise validated populations, translation, cultural adaptations, number of items, constructs measured, response options, clinically relevant cutoff scores, estimated completion times, and practical information about licensing fees and format. The measures represented in **Tables 1, 2, and 3** have been used across multiple countries throughout North America, South America, Europe, the Middle East, Africa, and Asia, and they are organized according to clinical and research purposes. Given that screening would be the first step in determining the presence or severity of CRF, measures

that serve this purpose are listed first. The measures that support further evaluation when screening results are moderate or severe are listed next.

The validated measures included in **Tables 1, 2, and 3** are grouped based on common characteristics and are divided into 3 categories. Category 1 (**Table 1**) includes measures for screening, category 2 (**Table 2**) includes unidimensional measures, and category 3 (**Table 3**) includes multidimensional measures. The categorization has 1 exception: We present the Measure Yourself Concerns and Wellbeing (MYCaW) measure on its own due to its unique properties. An outlier of the screening group, the MYCaW instrument¹⁴⁵ screener asks the patient to report their most important concerns in their own words. Similar to assessments found in the UK eHealth care agenda, an advantage of the MYCaW scale is that it empowers patients to participate in their own health by specifying fatigue/weakness as 1 of the 2 concerns and then assessing the extent that the fatigue bothers them on a 0- to 6-point scale. This scale highlights the patient's subjective interpretation of the impact of fatigue. A drawback to the MYCaW approach is the difficulty of analyzing heterogeneously reported symptoms.

Single-item measures

Category 1 measures used for screening take no more than 2 minutes to complete. Measures in this category include Clinical Significance, Fatigue Thermometer, and the Zung Self-Rating Depression Scale. Studies have validated the Clinical Significance tool in patients diagnosed with a solid tumor, including lymphoma, at any stage with an ECOG score of 0 to 3; the Fatigue Thermometer has been validated in adolescent and young adult survivors of brain tumors. The NCCN recommends use of a single-item screener question to screen patients for fatigue at regular intervals using age-appropriate measures.¹ Kirsh et al⁷⁹ validated the single fatigue item of the Zung Self-Rating Depression

Scale in ambulatory oncology patients undergoing treatment for malignancy. The overall benefit of single-item screening measures is that they offer quick, clinically meaningful cutoffs to determine if further evaluation is warranted. However, it is essential to not rely on these measures in isolation. They do not provide a thorough assessment of CRF across the physical, emotional, and cognitive domains of interest. Additionally, there may not be well-established clinical cutoff scores with known sensitivity and specificity in a given population.

Multi-item, unidimensional instruments

Category 2 includes multi-item, unidimensional instruments that are well known and often used, such as the Functional Assessment of Chronic Illness Therapy – Fatigue, and the Profile of Mood States – Fatigue subscale (POMS-F). These instruments contain multiple items designed to measure 1 CRF dimension. The ESAS-r independently measures a range of symptoms, one being fatigue or tiredness. The Four Item Fatigue Scale (FIFS) has the least number of items in this category and therefore has the least patient burden. Researchers found the FIFS to have concurrent validity with the BFI in the context of changes in CRF over time and severity in patients with advanced cancer being treated in palliative medicine; however, the FIFS requires further test-retest reliability.⁹¹ With 7 items, the POMS-F instrument has the second-least number. Like the FIFS, the POMS-F is exceptional for reducing patient burden and has been validated in breast cancer patients.⁹⁶ The benefits of these multi-item, unidimensional tools are that they use multiple items to assess CRF while demonstrating reliability and validity in relation to other known measures. Despite these benefits, however, unidimensional instruments can be limiting, because the scope of measurement is only the physical impact of fatigue, excluding its emotional and cognitive impacts.¹⁴⁶

TABLE 2. Category 2 Validated Patient-Reported Cancer-Related Fatigue Assessment Instruments

Instrument name	Validated population	Translation and/or cultural adaptation validation	# of items	Constructs measured	Response options; recall	Clinically relevant cutoffs	Estimated completion time	Practicalities
Category 2: Multi-item, unidimensional instruments								
ESAS-r ⁸²	Palliative patients, ambulant patients, mixed population	Mapi Research Trust translated into more than 20 languages ⁸³⁻⁸⁹	9	Severity of symptoms: pain, activity, nausea, depression, anxiety, tiredness, lack of appetite, well-being, shortness of breath ⁹⁰	Visual or numeric rating scale of 0-10; recall period = "now."	(Japanese) severe = 5-7; moderate/severe = 3-4 ⁸⁷	10 minutes	No cost, paper-and-pencil
FIFS ⁹¹	Advanced cancer, inpatient and outpatient settings	No data	4	Severity ranked as better, worse, or the same: over time	Likert-style and numeric rating scale of 0-10; evaluative responses	No data	>5 minutes	No cost; paper-and-pencil or electronic
FACIT-Fatigue ⁹²	Active treatment, palliative care, survivor, mixed cancer population	Iranian, ⁹³ Chinese, ⁹⁴ Arabic ¹⁰	13	Physical and functional effects of fatigue; in relation to anemia	5-point Likert-type scale; 7-day recall	<34 = relevant fatigue	>5 minutes	Licensing required, paper-and-pencil or electronic, face-to-face interviews, or telephone interviews
POMS-F ⁹⁵	Breast cancer, multiple cancer types	No data	7	Reflects mood states	Items rated on a 0-4 scale; recall period: over the past week	Scores range from 0-28; higher score = higher fatigue. Cutoff scores: ≥7 and <50 ⁹⁶	5-7 minutes	Use requires a fee; paper-and-pencil or electronic
VAS-F	Aged 18-55 years ⁹⁷	No data	18	Severity	An "X" along a line: one end = "not at all tired"; other end = "extremely tired."	Score, 0-100	5-10 minutes	No cost; paper-and-pencil

ESAS-r, Edmonton Symptom Assessment Scale, revised; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy – Fatigue; FIFS, Four-Item Fatigue Screening; POMS-F, Profile of Mood States – fatigue subscale; VAS-F, Visual Analogue Scale to Evaluate Fatigue Severity.

Multi-item, multidimensional instruments

Category 3 includes multi-item, multidimensional instruments used for assessing CRF. They are multidimensional in that each measure combines a variety of dimensions known to characterize CRF in different ways. The dimensions measured include physical, emotional, cognitive, impact on functioning, severity, interference, HRQOL, vigor, associated symptoms, and patterns of fatigue. BFI is a category 3 instrument that clinicians and researchers commonly use. In contrast to category 1 and 2 instruments, those in category

3 provide a more thorough assessment of the patient experience of CRF, given its multidimensional measures. For example, in category 3, the 30-item European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cancer (EORTC QLQ C-30), fatigue severity is assessed with items No. 12 (“Have you felt weak?”) and No. 18 (“Were you tired?”), with scores ranging from 0 to 100. With its 1-week perspective, the EORTC QLQ C-30 significantly adds to the 24-hour score findings of the ESAS-r while being more patient centered and less symptom oriented. Another

advantage of the EORTC QLQ C-30 is that it includes symptom scales (including fatigue) as well as functional scales. The inclusion of symptom and functional scales allows clinicians and researchers to see trends across dimensions, which allows for greater understanding of CRF in association with other symptoms and QOL concerns in and across different scales. Furthermore, multidimensional instruments help inform interventional studies. Findings from these instruments provide in-depth data regarding changes in severity and the dimensions most impacted by the intervention.

TABLE 3. Category 3 Validated Patient-Reported Cancer-Related Fatigue Assessment Instruments

Instrument name	Validated population	Translation and/or cultural adaptation validation	No. of Items	Constructs measured
Category 3: Multi-item, multidimensional instruments				
BFI ⁶⁰	Palliative, survivor, mixed cancer population	Arabic, ⁹⁸ Ethiopian, ⁹⁹ Italian, ¹⁰⁰ Indonesian ⁹⁴	9	Fatigue severity; fatigue interference; mild, moderate, severe
CFQ 11 ¹⁰¹	Breast cancer ¹⁰²	Brazil (primary care) ¹⁰³	11	Clinically significant fatigue, severity, physical fatigue, mental fatigue ¹⁰⁴
EORTC QLQ-FA12 ⁰⁵	Curative and palliative, survivor, lung cancer, bone marrow transplant, metastatic cancer	No data	12	Used alongside the EORTC QLQ-C30; physical, emotional, and cognitive dimensions
EORTC QLQ C-30 ⁰⁶	Metastatic breast cancer, prostate cancer, gynecological cancers	Moroccan, Arabic, ¹⁰⁷ Indonesian, ¹⁰⁸ Chinese ¹⁰⁹ ; translated into 54 languages ¹¹⁰	30	For clinical research; 5 functional scales, 3 symptom scales, a global health status/QoL scale, and 6 single items
FSI ^{112,113}	Breast cancer and mixed cancer population	No data	14	Fatigue severity, fatigue frequency, perceived interference associated with fatigue, daily pattern of fatigue
FSS ⁹	Breast and prostate cancers, ¹¹⁴ advanced cancer ¹¹⁵	Translations to Maltese, Arabic, Persian, Turkish, Portuguese, Norwegian, Danish, Swiss, and Swedish are for noncancer populations	8	Physical functioning; activities of daily living; sleep
MDASI ⁶¹	Patients with cancer	Arabic, ¹¹⁶ Chinese, ¹¹⁷ Filipino, ¹¹⁸ French, ¹¹⁹ Greek, ¹²⁰ Japanese, ¹²¹ Korean, ¹²² Russian ¹²³	13	Severity and interference
MFI ¹²⁴	Mixed population, active treatment, palliative, survivor	Swedish, ¹²⁵ French, ¹²⁶ Hindi, ¹²⁷ Chinese, ¹²⁸ Polish, ¹²⁹ Brazilian, ¹³⁰ French-Canadian ¹³¹	20	5 dimensions of fatigue: general, mental, physical, reduced motivation, reduced activity
MFSI-SF ³²	Mixed cancer population	Chinese, ¹³³ Italian ¹³⁴	30	5 subscales: general, physical, emotional, mental, vigor
PFS-R ¹³⁶	Lung and breast cancer patients, breast cancer survivors 3 years from diagnosis	Spanish, ¹³⁷ Italian, ¹³⁸ Dutch, ¹³⁹	22	4 subscales: behavioral, affective, sensory, cognitive/mood
PFS-12 ¹⁴⁰	African American and Caucasian breast cancer survivors 3 years from diagnosis	No data	12	4 subscales: behavioral, affective, sensory, cognitive/mood
PROMIS F-SF	Adults, across all cancer types	No data	7	Frequency, duration, and intensity; impact on physical, mental, and social activities
SF-36	Not cancer-specific but has been used in the breast, lung, gastrointestinal, lymphoma genitourinary, hematological cancer populations ¹⁴³	Turkish, ¹⁴⁴ Italian ⁷⁸	36	Physical function, bodily pain, limitations, personal or emotional problems, emotional well-being, social function, energy/fatigue, and general health perception; perceived change in health

BFI, Brief Fatigue Inventory; CFQ 11, 11-item Chalder Fatigue Scale; EORTC QLQ C-30, 30-item European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cancer; EORTC QLQ-FA12, 12-item European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cancer Related Fatigue; FSI, Fatigue Symptom Inventory; FSS, Fatigue Severity Scale; IVR, interactive voice response system; MDASI, MD Anderson Symptom Inventory; MFI, Multidimensional Fatigue Inventory; MFSI-SF, Multidimensional Fatigue Symptom Inventory – Short Form; PROMIS F-SF, Patient Reported Outcomes Measurement Information System, Fatigue – Short Form; PFS-12, Piper Fatigue Scale-R; Piper Fatigue Scale-12; QOL, quality of life; SF-36, RAND 36-Item Short Form Health Survey.

^aLimited use in patients with cancer.

	Response options; recall	Clinically relevant cutoffs	Estimated completion time	Practicalities
	Numeric 0-10 scales. 0 = no fatigue, 10 = as bad as imaginable (questions 1-3). 0 = does not interfere, 10 = completely interferes (questions 4a-f); 24-hour recall	Mild, 1-3 (model 1) or 1-4 (model 2); moderate, 4-6 (model 1) or 5-6 (model 2); severe, 7-10 (models 1 and 2); German cutoffs vary	>5 minutes	Academic use, no cost; commercial use, licensing fee required; interview with research staff, electronic, or IVR without research staff
	2 scoring systems: yes/no and 4-point scale	Not fatigued, ≤3; severe fatigue, ≥4	10-12 minutes	No cost; paper-and-pencil
	4-point Likert-type scale; in the past week	No proposed cutoff values; not used for diagnostic purposes	10-12 minutes	No cost for academic use; fee for commercial use; paper-and-pencil or electronic
	4-point Likert-type scale; higher scores = better function; recall: within the "past week"	100: sadness; 90: physical and role function and QOL; 10: pain and fatigue ¹¹¹	10 minutes	No cost for academic use; fee for commercial use; paper-and-pencil or electronic
	Numeric rating scale, 0-10	≥3 average fatigue severity item or mean score ≥3 fatigue severity; in the last week	5 minutes	Registration required; paper-and-pencil
	7-point Likert scale; numerical; over the last week	The higher the score, the more severe the fatigue; minimum score 9, maximum score 63	>10 minutes	No cost; paper-and-pencil
	13 core items, presence and severity of symptoms and level of symptom interference with function; 24-hour recall	5-6, moderate; ≥7, severe	10-12 minutes	No cost for academic use; licensing fee required for commercial use; paper-and-pencil, electronic, and telephone-based IVR
	Likert-type scale	Higher scores reflect greater severity	>5 minutes	No cost for academic use
	Likert-type scale; 7-day recall period	Total fatigue, 24 -96; no cutoff scores ¹³⁵	>10 minutes	No cost; paper-and-pencil
	Scale of 0-10; recall concerns current experience	Higher scores reflect greater severity	>10 minutes	No cost; paper-and-pencil
	Scale of 0-10; recall concerns current experience	0, no fatigue; 1-3, mild fatigue; 4-6, moderate fatigue; 7-10, severe fatigue ¹⁴¹	5 minutes	No cost; paper-and-pencil
	5-point Likert-type scale; 7-day and a daily recall (since waking up)	From 7-35, higher scores indicate more significant fatigue ¹⁴²	>10 minutes	No cost; paper-and-pencil (short forms and profiles only), electronic
	Combination of Likert scale questions, yes/no questions, and multiple-choice questions. Recall period = general, ranging from "now" to "4 weeks ago."	High score = more favorable health state.	10 minutes	No cost; electronic and paper-and-pencil versions available



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TABLE 4. CRF PRO Recommendations

NCCN single-item tool	Indicates clinical significance
BFI	Offers fast, easy, helpful cutoffs and measures of both severity and daily functioning interference
MDASI	Robust CRF measure; psychometrically rigorous translations can be used to gather symptom severity and interference ratings that can be comparably interpreted across patient nationalities
ESAS-r	Robust CRF measure; multidimensional; offers multiple time perspectives; complements the MYCaW
PROMIS–Fatigue Short Form	Advantageous for conducting comparisons and identifying norms across populations
MYCaW	Easy to implement in clinical practice; supports patient reports of CRF multidimensionality; offers multiple time perspectives; complements the ESAS-r
EORTC QLQ-C³⁰	Good outcome measure for QOL during certain time points—such as pre- and post therapy; supports comparative research

BFI, Brief Fatigue Inventory; CRF, cancer-related fatigue; ESAS-r, Edmonton Symptom Assessment Scale; EORTC QLQ C-30, 30-item European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Cancer; MDASI, MD Anderson Symptom Inventory; MYCaW, Measure Yourself Concerns and Wellbeing; NCCN, National Comprehensive Cancer Network; PRO, patient-reported outcome; PROMIS F-SF, Patient Reported Outcomes Measurement Information System, Fatigue – Short Form; QOL, quality of life.

It can be argued that despite the additional data that category 3 measurements provide, they may fail to provide evidence for the variability that can occur across these dimensions and constructs of CRF. Another potential disadvantage to using multidimensional scales is their length. The longest category 3 instruments include 36 items, and this length can be burdensome for fatigued patients no matter what their disease stage. In addition, scoring larger instruments by hand can be demanding for clinicians. When deciding on a measure to use, it is essential to consider all these factors and their impact on the study objectives.

Proposals for Standardization

Based on the available results of psychometric and population-based studies, we recommend the following PROs for measuring CRF (Table 4): The NCCN single-item tool is recommended for measuring clinical significance, and the BFI offers fast, easy, helpful cutoffs and measures of both severity and daily functioning interference. Further, when assessing multidimensional qualities and fatigue symptom cluster is necessary, either the MDASI or ESAS-r offers a robust CRF

measure. Furthermore, psychometrically rigorous translations of the MDASI into various non-English versions can be used to gather symptom severity and interference ratings that can be comparably interpreted across patient nationalities.⁷² The rigorously developed Patient Reported Outcomes Measurement Information System (PROMIS) measurement system, including the PROMIS–Fatigue Short Form, has advantages related to comparison and norms across populations. The MYCaW has been used in specialized cases^{73-75,145} and studies have demonstrated that this tool is easy to implement in real-life clinical practice, and like the ESAS-r, offers multiple time perspectives, and complement each other by viewing CRF multidimensionally. Results of the EORTC QLQ-C30 are a good outcome measure for QOL during certain time points—such as pre- and post therapy—and are good for comparative research; however, they are limited in terms of longitudinal fatigue assessment.

Complementary measurement use occurs when clinicians find it important to combine a symptom perspective (eg, ESAS-r) and a patient-centered perspective (eg, MYCaW) while assessing impacts to QOL (eg, EORTC QLQ-C30).

While single-item screening measures are quick, they are limited in assessing the multiple domains of CRF yet completing longer instruments may be problematic and burdensome for patients with advanced cancer.

As we have shown, when the multidimensional nature of CRF is considered in addition to concerns such as recall period, treatment regimen, and the availability of validated measures that have been translated, selecting subjective CRF measures can become complex. This creates barriers for clinicians who attempt to integrate CRF into their decision-making and instead are faced with a lack of meaningful, interpretable summary measures.⁵⁹ For these reasons, we suggest the following areas in which future research can help improve the use of PROs and our understanding of CRF.

Future Directions

Future research should explore several areas of CRF measurement and PRO use. From a patient perspective, the CRF assessment should include measurements across diverse populations and consider patient burden. The National Cancer Institute has recently implemented the Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE), which addresses this consideration. This recently validated PRO instrument is for clinical trial use in reporting symptomatic adverse events (AEs); it minimizes patient burden by shortening HRQOL questionnaires.¹⁴⁷ In total, a library of 124 PRO-CTCAE items were created that represent 78 symptomatic toxicities from which researchers can choose the relevant items depending on the study population. The PRO-CTCAE was created to enhance the precision and patient-centeredness of AE reporting.¹⁴⁸ Studies using the PRO-CTCAE library for CRF are beginning to emerge, suggesting this as a potential future direction for clinical trial research.

Additionally, researchers should evaluate patient preferences for handwritten

vs electronic questionnaires. From a measurement consideration, researchers can explore completion times and completion rates for each of the validated fatigue PRO measures in real-world settings and how these may differ in electronic data collection compared with paper-and-pencil administration.

When considering measures in the design phase, researchers could include comparisons of instruments and where needed, provide cross-cultural validity to support international clinical guidelines.⁷² Additional research investigating patient preferences for specific CRF PRO instruments may find that patient preferences differ or align with researcher and clinician preferences. Future studies should also examine the impact of whether a questionnaire is free for public use or requires payment for licensing on the uptake of measures.

When undertaking CRF research, investigators should consider various methodologies that enrich the applicability and implementation of research outcomes in real-life integrative oncology (IO) clinical practice. For example, as in studies of supportive and palliative care, IO pragmatic studies need to respect the typical IO setting regarding patient preferences, patient-tailored treatment, and multimodal IO programs, as well as questions on how to maintain adherence and continuity of care. In doing so, pragmatic research will complement randomized control trials' line of research.

CRF researchers should also consider broadening their focus—not just examining the impact of CRF on patients' QOL, but also including additional oncology parameters. Such future studies could include measuring the impact of CRF on adherence to oncology treatment protocols¹⁴⁹ and assessing the cost effectiveness of CRF analysis. Studies that explore CRF should examine its impact on, or association with, other symptoms, relationships, employment, and absenteeism/presenteeism; related outcomes should be included in studies when feasible.

These future research considerations increase the possibility for guidelines on CRF and IO to include rigorous pragmatic and controlled research in their inclusion criteria, even if not randomized, to address the real-life IO setting in leading cancer centers in the US and internationally. In addition, publications could include studies where CRF is the primary clinical outcome and studies that assess CRF-related QOL-concerns (eg, pain, insomnia, anxiety, appetite) in a broader patient-centered context. By recognizing these criteria, clinicians and researchers can better understand the overlap across the multidimensional aspects of fatigue.

Conclusions

This review introduced CRF, summarized the literature concerning CRF prevalence and impacts, challenges for diagnosis and treatment, issues with CRF measurement, the most widely reported CRF PRO measures, and provided recommendations on validated CRF PRO measures use based on specific contexts.

CRF is a complex and persistent symptom that impacts many patients with cancer throughout their disease experience. Like many symptoms, CRF is predominantly assessed through subjective PRO instruments for a variety of reasons across clinical practice and research. The more complex the measure and the more domains that are assessed, the greater the challenge of measuring CRF can become. As research progresses, it is increasingly evident that objective measures are needed to understand CRF etiology; such measures are instrumental in developing effective CRF interventions. In this effort, research utilizes objective lab- and performance-based measures, but it must be noted that objective measures, such as handgrip strength, lean body mass, and maximal inspiratory pressure, should not replace subjective measures.¹⁵⁰ Rather, objective and subjective measures can work in a complementary way to support patient care.

Presenting the criteria for how researchers make measurement decisions in their published findings would further support a collective move toward a core group of measures that will improve the ability to compare clinical and research outcomes with one another. With this move toward standardization, we anticipate that our understanding of CRF and ways to effectively measure CRF will positively impact patient care with detailed guidelines that assist in improved CRF management and intervention. ■

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