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ASCPRO Recommendations for the Assessment of Fatigue as an Outcome in Clinical Trials

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Abstract

Context—Development of pharmacologic and behavioral interventions for cancer-related fatigue (CRF) requires adequate measures of this symptom. A guidance document from the Food and Drug Administration offers criteria for the formulation and evaluation of patient-reported outcome measures used in clinical trials to support drug or device labeling claims.

Methods—An independent working group, ASCPRO (Assessing Symptoms of Cancer Using Patient-Reported Outcomes), has begun developing recommendations for the measurement of symptoms in oncology clinical trials. The recommendations of the Fatigue Task Force for measurement of CRF are presented here.

Results—There was consensus that CRF could be measured effectively in clinical trials as the sensation of fatigue or tiredness, impact of fatigue/tiredness on usual functioning or as both sensation and impact. The ASCPRO Fatigue Task Force constructed a definition and conceptual model to guide measurement of CRF. ASCPRO recommendations do not endorse a specific fatigue measure but clarify how to evaluate and implement fatigue assessments in clinical studies. The selection of a CRF measure should be tailored to the goals of the research. Measurement issues related to various research environments were also discussed.

Conclusion—There exist in the literature good measures of CRF for clinical trials with strong evidence of clarity and comprehensibility to patients, content and construct validity, reliability, sensitivity to change in conditions in which one would expect them to change (assay sensitivity), and sufficient evidence to establish guides for interpreting changes in scores. Direction for future research is discussed.

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Keywords

Cancer-related fatigue; self-report measures; clinical trials; patient-reported outcomes

Introduction

Fatigue is the most common and distressing symptom related to cancer and its treatment (1). Prevalence estimates of cancer-related fatigue (CRF) during treatment range from 25% to 99% depending on the sample and method of assessment (2). This symptom may be present at diagnosis, during treatment, chronically for some survivors, and/or at the end of life. CRF is known to affect quality of life, functional outcomes including work and, possibly, survival. Fatigue is distinct from many other cancer-related symptoms because it is *not* unique to cancer or its treatment. Almost everyone experiences fatigue every day, blurring the line between the normal occurrence of fatigue and the pathological symptom of CRF. Despite a large body of research that has shed light on the problem of CRF and its management, there are gaps in our scientific understanding of this symptom.

Although hundreds of thousands of cancer patients are faced with debilitating CRF at various stages in their illness, research into the efficacy of existing treatments and development of new treatments to reduce CRF has been slow. A major reason for lack of progress in this area has been the lack of consensus about how to conceptually define and measure CRF in clinical research. In contrast to other cancer-related symptoms, such as pain or nausea/vomiting, where conceptual definitions are almost intuitive and measurement strategies are more established, unresolved issues regarding the definition and measurement of CRF have been a major impediment to progress in establishing the most effective treatments to manage it.

Perfect and final conceptualization and measurement of CRF is not a realistic goal. But progress is needed so the people most at risk for CRF are not deprived of the benefits of new treatments that could relieve, minimize, or prevent the suffering associated with it. This need must be balanced against the danger of inaccurate or unclear understanding of CRF and the approval and use of inappropriate treatments for this symptom. In this paper, the authors address the tension between the goal of scientific rigor and the need for a realistic approach in measuring CRF; recommendations will be made for resolving this.

In 2006, clinical researchers from academia and the pharmaceutical industry joined with participants and observers from government agencies to address symptom-measurement issues related to clinical trials in cancer. This group—Assessing the Symptoms of Cancer using Patient-Reported Outcomes (ASCPRO) (3)—has the goal of developing recommendations for symptom measurement that promotes clinical research focused on cancer-related symptoms. The formation of ASCPRO was, in part, a response to the issuance of guidance by the U.S. Food and Drug Administration (FDA) about the use of patient-reported outcomes in labeling claims (4). The finalized guidance provides advice to the pharmaceutical industry about what FDA will look for in review of patient-reported outcomes, including symptom reports, to ensure adequate development, validity, reliability, and interpretability of these outcomes for regulatory decision-making about the safety and efficacy of treatments. Although the FDA guidance document is binding only to research conducted in support of labeling claims, the authors address some issues raised in the document that are also relevant to the broader academic and clinical research communities.

ASCPRO is indebted to the preceding efforts of the international networking groups, Outcome Measures in Rheumatology (OMERACT) (5) and the Initiative on Methods,

Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (6). These groups sought to improve the conceptualization and measurement of outcomes in clinical trials for rheumatology and pain management, respectively.

In 2007, a subgroup of ASCPRO members formed a Fatigue Task Force that comprised participants from academia, the pharmaceutical industry, clinical practice, patients and survivors, as well as observers from the National Institutes of Health (NIH) and FDA. The Fatigue Task Force held a series of meetings using a consensus-building process to make recommendations for the assessment of CRF in clinical trials. The purpose of this manuscript is to report the deliberations and consensus developed thorough this series of meetings.

Several topics were selected to provide a catalyst for discussion and consensus building about the assessment of CRF in clinical trials. These included: definition and conceptual model of CRF; characteristics of a good CRF measure; and unique issues in single-institution, multiple-institutional, and pharmaceutical trials. For each topic, the task force identified a diverse panel of experts to initiate the discussion. At the October 2007 meeting of the ASCPRO Steering Committee, the expert panel members made brief presentations of each topic followed by a lengthy discussion with the steering committee as a whole. Members of the Fatigue Task Force led each panel presentation and discussion. Efforts were made to represent the diversity of opinions and perspectives related to each topic.

Pursuant to the 2007 meeting, the Fatigue Task Force developed a consensus statement based on the deliberations at the meeting. This consensus statement was based on audio-recordings of the meetings that were transcribed, reviewed by the Fatigue Task Force members and discussed in several conference calls. The Fatigue Task Force convened again in June 2008 to review the consensus points and Task force members wrote sections of this manuscript.

At the outset, it was apparent that CRF was difficult to conceptualize from a measurement standpoint. There was considerable uncertainty and occasional disagreement within the working group about several issues including the definition, conceptual models of the phenomenon, appropriate research designs, and measurement methods. There was also substantial discussion, based on the FDA guidance document, about what a labeling claim for a treatment or product intended to reduce CRF might look like, and what type of measurement strategies would be needed to evaluate such a labeling claim. The conclusions and recommendations of the ASCPRO Fatigue Task Force are bulleted at the beginning of each section of the manuscript. A summary of the discussions that developed around each conclusion follows each conclusion point.

Definition and Conceptual Model of CRF

- The ASCPRO consensus definition of CRF is: the perception of unusual tiredness that varies in pattern or severity and has a negative impact on ability to function in people who have or have had cancer.
- CRF can be measured effectively in clinical trials as the sensation of fatigue or tiredness, impact of fatigue/tiredness on the patient's life, or as both intensity and impact of fatigue.
- For each study, a definition of CRF should be specified and a conceptual model that underlies the assessment of CRF for that study should be supplied.

Although fatigue is a familiar experience to almost everyone, CRF has been described in qualitative research as “nebulous” or “intangible” (7,8). Metaphorical descriptions of CRF

abound, suggesting that the phenomenon is not easily conveyed with direct observation-based statements and must be related to an experience that can be conveyed directly using simile or metaphor (1). Difficulty describing CRF has resulted in variability in defining and measuring this phenomenon.

Defining Cancer-Related Fatigue

The general concept of fatigue (not necessarily related to cancer) has been described conceptually in several ways. Clinical researchers emphasize the "subjective" experience or individual perception of fatigue or tiredness (9). In contrast, muscle physiologists view fatigue as a "performance decrement" that can be observed as reduced muscle strength or increased error rates on tasks requiring vigilance. CRF has also been described as a diagnosed condition. As proposed for the International Classification of Disease, 10th revision, the diagnosis of CRF is based on four criteria including indicators of symptom presence, distress or impairment, etiology related to cancer or cancer treatment, and absence of psychiatric disorder (10). In keeping with the current philosophy of symptoms as patient-reported outcomes, the ASCPRO Steering Committee addressed CRF as a subjective experience that requires patient self-report to identify and describe it.

A literature review of conceptual definitions of CRF was conducted revealing 24 definitions posed by experts (8,11-35). An iterative process was used to identify unique characteristics contained within each definition to describe the concept. Seven characteristics were identified: subjectivity, unusualness, physical sensation, unpleasant emotions, impact on ability to function, decreased cognitive ability, and temporal variability. Words and phrases in the definition that indicated the presence of each characteristic and the percentage of definitions that included each characteristic are presented in Table 1.

There was both redundancy and variability among the definitions with regard to the characteristics of CRF. In 92% of the definitions, physical sensations including tiredness, decreased energy (18,19,36), and exhaustion were used to characterize CRF (34). Sixty-six percent of the definitions included the characteristic of decreased functioning. Examples included decreased capacity for work (14) and difficulty completing tasks (27). Other characteristics cited in more than half of the definitions were its subjective nature (58%), temporal variability (58%), and unpleasant emotions related to it (54%).

There was also variability among definitions with regard to the characteristics described. Less than 50% of the definitions characterized CRF as unusual or different from fatigue experienced by healthy people. Also cognitive decrements due to CRF were identified in only 46% of the definitions. Finally, it was noted that the definition of CRF proposed by the consensus guidelines panel of the National Comprehensive Cancer Network (NCCN) has been revised and amended with almost every new version of the guidelines, illustrating an evolving consensus about the definition of CRF (34).

Based on the discussion of conceptual definitions, the ASCPRO consensus definition of CRF is: the perception of unusual tiredness that varies in pattern and severity and has a negative impact on ability to function in people who have or have had cancer. The panel agreed that physical sensations and decreased functioning are hallmark characteristics of CRF.

A Conceptual Model of Cancer-Related Fatigue

Coming to agreement about the definition is only the first step in identifying an appropriate measure of CRF. The definition establishes the key elements of the concept. The next step is to create a conceptual model that demonstrates links between the elements of the concept (CRF) and its relationship to other concepts including outcomes of interest. Once a model

has been established, the measurement of the concept becomes clearer. An effective conceptual model guides the selection of measures. Using systematic methods to guide assessment offers the greatest likelihood of achieving useful and interpretable outcomes data from clinical trials. In the case of instrument selection or development for clinical trials, the conceptual model determines both the concepts that must be captured to fully characterize a symptom such as CRF and how the items should be summarized in scores.

ASCPRO developed a conceptual model to describe the features of CRF that would be useful in critically evaluating proposed assessments and study designs to evaluate changes in CRF (Figure 1). The traditional symptom measurement model assumes that functional changes result from symptoms that interrupt normal function, e.g., the presence of knee pain causes a person to avoid running or climbing stairs. In the case of CRF, the conceptual distinction between symptom and functional impairment is blurred (13,37,38). Qualitative descriptions of CRF illustrate this point. People with CRF have reported:

- physical sensations described as feeling tired or weary, lacking energy, having heaviness in limbs (39,40)
- mental sensations such as feeling emotionally drained, feeling mentally exhausted, having difficulty motivating themselves (8,25,39,41)
- impaired physical functioning reflected in lack of usual strength or stamina during activities (26,42)
- impaired cognitive functioning including problems remembering things, inability to concentrate or think clearly (11,23,25)

These sensations and functional effects of CRF lead to perceived worsening of overall health and health-related quality of life. Individuals perceive their tiredness or weakness as abnormal because it makes things they would do ordinarily more difficult or impossible to do (23,26,42). This explains why the sensation of tiredness or lack of energy has been so highly correlated with functional limitations as to appear unidimensional. In contrast to the usual experience of tiredness, individuals with cancer emphasize the unusual character of their tiredness that results in unexpected limitations in the ability to do normal activities (26,39).

Given the interdependence of functioning and sensation in the perception of CRF, the ASCPRO conceptual model describes CRF as the sensation of tiredness and/or the extent of limitation in functioning due to tiredness. This conceptualization does not preclude measurement purely as intensity of tiredness, nor does it require measurement of both intensity and impact. The model simply reflects the empirical evidence – qualitative and quantitative – that for tiredness to be understood as pathological, it is often useful to link it with impact on functioning. Based on the evidence that these characteristics have a strong correlation with each other (r = .79 to .95) (43-45), the final consensus of the Fatigue Task Force is that CRF is a unidimensional construct (at least psychometrically) despite the conceptual distinctions between sensations and impact on functioning.

Selecting an Appropriate Measure of CRF

- The characteristics of a good CRF measure are the same as those for other patient-reported outcome measures. It requires strong evidence of clarity and comprehensibility to patients, content and construct validity, reliability, sensitivity to change under conditions in which change is expected, and sufficient evidence to guide interpretation of changes in scores.

- Many good measures of CRF are available for use in clinical trials. ASCPRO recommendations are not intended to dictate a specific CRF measure but to clarify how to evaluate and implement CRF assessments in clinical studies.
- Study intent is critical to the selection of a CRF measure. Selection of a CRF measure should be based on what the intervention or product is likely to influence – reducing CRF as a symptom of disease or other treatments, producing less impact on functioning, or preventing onset or worsening of CRF sensations.

As with measuring any other symptom, the decision to assess CRF in a trial involves careful planning to define the salient aspects to be measured; considering optimal study designs to minimize confounding; selecting an appropriate CRF instrument; identifying appropriate time points in the study to assess CRF; and selecting appropriate statistical methods to model CRF over time. Central to this planning effort is the development of hypotheses about the expected level and change in CRF that will drive the study design, questionnaire selection, and interpretation of results.

Study Design Considerations

Establishing a Conceptual Framework—Recognizing the lack of a universally-accepted definition of CRF, the investigator must provide a clear conceptual definition, ideally one that was developed from empirical studies of CRF in similar populations and published in the scientific and medical literature. This definition will drive the measurement approach and is critical for interpreting the study findings. Key information to extract from the definition includes how the target population experiences CRF – physically, emotionally, and/or cognitively. Does the definition include aspects of CRF severity, impact on functioning, or both? Does the definition clarify whether these aspects can be captured by a single (i.e., unidimensional) score or suggest the need for multiple scores to summarize sensations separately from their impact on functioning? Further, the definition or the study hypotheses may indicate causal attribution if CRF is due to disease, treatment, or both. Study hypotheses should also indicate if CRF will be reported as average, worst, or current as this decision will determine item wording.

Controlling Confounding Factors—Appropriate controls for potential confounding factors include study design considerations. Sample selection approaches allow the investigator to control for the type of disease, stage of disease, time since diagnosis, co-morbid condition, patient demographics, and functional status, any of which could influence the experience of CRF. The population studied will strongly influence the conclusions one can draw about the effectiveness of an intervention or the drug claim that is allowed. Randomization and/or stratification techniques for assignment to treatment arm and use of a control arm could also reduce confounding. The investigator should also measure other symptoms that could be confounded with CRF such as sleep disturbance, emotional distress and/or depression, anorexia, and anemia.

CRF Questionnaire Considerations

There is no “gold standard” instrument to measure CRF. A host of assessments have been used to measure CRF, many of which have been used in clinical trials (Table 2). Several recent reviews of published CRF assessments highlight the strengths and weaknesses of each available assessment (40,46-51). These reviews confirm the Fatigue Task Force recommendations that researchers should pick the most appropriate instrument to achieve the study goals.

CRF assessment can be as simple as a single question about severity of tiredness rated on a 0—10 numeric rating or 100mm visual analog scale. This type of assessment minimizes

participant burden if properly implemented and can be used in cancer trials to monitor CRF as a secondary endpoint, safety indicator, or when severity of CRF is the only attribute of interest.

When CRF is the primary endpoint of the investigation, a more comprehensive assessment of CRF may be appropriate to ensure that important aspects of this symptom are assessed. The many available measures of CRF (46) vary greatly in their properties including length, construct definition, dimensionality, and evidence of validity. Table 3 provides a list of desirable attributes to consider in selecting a questionnaire although not every instrument will reflect every attribute. A CRF measure should be selected to operationalize the concept and match the needs of the study including the appropriateness of the instrument to be used as an efficacy or safety endpoint, and/or as a screener for study eligibility.

Validity and Reliability—An effective CRF measure should have evidence of validity, reliability, and sensitivity; it should also capture the experience of CRF with minimal respondent burden. There are several types of validity. Content validity is the extent to which the items and scales reflect the attributes indicated in the CRF definition. Construct validity is the extent to which a measure "behaves" in a way consistent with theoretical hypotheses; it represents how well scores on the instrument are indicative of the CRF construct (52). The two types of reliability (or precision) relevant to patient-reported CRF are internal consistency and test-retest reliability. Internal consistency captures the strength of associations among multiple CRF items in a single assessment. Reliability and standard error of measurement are inversely related; thus a precise instrument has low measurement error. Test-retest reliability captures the stability of CRF over repeated assessments. Because lower correlations could be an artifact of the instrument or variation in CRF over time, it is important to select measurement points for test-retest reliability in which little change would be expected.

Recall Period—A critical issue for capturing the experience of CRF is the reference or recall period used by the questionnaire. Studies have shown that recall bias increases as the reference period gets longer. Regulatory agencies have encouraged assessments that ensure patients report "current state" rather than "average experience over…" (4). Real-time data capture methods, including daily diaries and electronic assessment have been used to capture the variability of episodes of CRF. However, it is important to keep in mind that daily assessments can add burden to both the patient and administrator, increase missing data, and may not provide an accurate measure of high or low severity of CRF experiences if not timed correctly. CRF may fluctuate throughout the day and throughout the course of cancer treatment. Capturing variability, limiting patient burden, and minimizing missing data are serious challenges.

Some studies have shown that 3- and 7-day recall correlate highly with daily diaries. However, requiring respondents to aggregate experiences of CRF and select a response that represents their average or worst CRF experience over longer periods of time can increase bias (53). More research needs to be conducted to compare recall periods to real time data on CRF, and identify optimal strategies to capture patient experiences that enhance patient care and inform decisions on the relative benefits of interventions.

Single versus Multiple Items—CRF questionnaires vary in length. Single-item CRF measures have low response burden which is ideal for longitudinal trials with multiple assessments. Further, empirical studies have found high correlations between the single and multiple-item CRF scales (32,54). Multiple-item measures increase assessment time. However, a well constructed scale will have greater precision across a greater range of severity. Further, multiple-item measures better respond to issues of content validity as they

can capture related but separate attributes of the symptom (e.g., fatigue sensation and impact).

The decision to use a single- or multiple-item CRF measure will likely be case-specific. Unique study designs could call for both types of measures with a single CRF item on a daily diary and a multi-item measure administered at baseline and one-week recall periods (4). Also, projects like the Patient-Reported Outcomes Measurement Information System (PROMIS) (55) could provide a solution to the controversy by delivering individually-tailored assessments, through computerized-adaptive testing (CAT), with brief, valid, and precise measures of CRF.

Scoring—Scores on the CRF measure should be interpretable with regard to the metric change that represents a clinically meaningful change in CRF severity as opposed to random error. Considerable efforts recently have focused on establishing minimally important differences (MIDs), defined as the smallest change in health status that is perceived by patients and/or indicates treatment benefit or harm (56-60). Study hypotheses should indicate the MID with a strong rationale based on the literature.

Timing of Assessments—Timing of data collection is critical to capture changes in CRF during the course of a study. A strong rationale for the timing of assessments that both accounts for the temporal nature of CRF and links it to key milestones within the study should be provided. A careful balance has to be achieved so that there are enough data points to capture the CRF trajectory while minimizing burden on patients and administrators which could result in missing data. Technology like interactive voice response (IVR) and web-enabled devices should be considered for studies with frequent assessments.

Measurement Considerations in Different Environments

- Investigators should consider the particular requirements of various funding sources as well as the environment in which the research will be conducted when selecting a CRF measure.

Clinical trials of drugs or behavioral therapies for CRF have similar goals: to determine the efficacy of a specific intervention to alleviate CRF. However, differences in the environment in which the trial is conducted, the type of intervention (drug/device or behavioral approach), and the agency or committee evaluating scientific merit are likely to place different demands on the investigator with regard to the measurement of CRF.

The NIH and National Cancer Institute (NCI) provide funding support for clinical trials focused on prevention and treatment of cancer, rehabilitation from cancer, and the continuing care of cancer patients and families. Cooperative agreements (61) and grants are the two key funding mechanisms that support clinical trials of CRF. Because the NIH/NCI research mission is quite broad, generally excluding product development and regulatory responsibilities, investigators have a fair amount of latitude in designing their clinical trials. However, there are differences based on the type of trial.

Single-Site Clinical Trials

Because the emphasis of NIH/NCI is the generation of new knowledge, investigators seeking funding to conduct a clinical trial need to consider several issues with respect to the selection of CRF measures. Questions will be raised during peer review process about the conceptualization of CRF, congruence between the selected CRF measure and the conceptual model, and the rationale for additional measures to evaluate co-occurring symptoms (such as sleep disturbance, anxiety, depression, or pain). A review of the publicly

available clinical trials database, Clinicaltrials.gov (62) using the terms ‘cancer’ and ‘fatigue’ showed that NCI is currently supporting 30 clinical trials and the National Institute of Nursing is supporting two. Of the 30 NCI trials, CRF is the primary endpoint of eighteen trials. Many of the trials are testing behavioral interventions, such as exercise, cognitive behavioral approaches, yoga, acupuncture, and massage, and the remaining studies are testing pharmacologic agents and dietary supplements. The trials often have secondary aims, usually focused on examining the impact of CRF on one or more quality of life domains, correlating CRF with one or more physiologic endpoints, and/or assessing performance of several measures of CRF. Thus, participants may be asked to complete a significant battery of measures.

Multiple-Site Clinical Trials

For projects that will be conducted in multiple settings, for example, in the Community Clinical Oncology Programs (CCOP), careful consideration must be given to maintaining a reasonable balance between the need for brief measures to minimize participant and/or staff burden and the need to measure the CRF construct adequately and appropriately. Community physicians who will be enrolling participants have input into the design and methods of CCOP clinical trials. Their emphasis is on broad eligibility and simplicity of study design that does not require special resources for intervention or data collection. An important question in this context is whether and how the scientific goals of the clinical trial can be reasonably accomplished in the multi-site environment.

Pharmaceutical Company Trials

The construction of labeling claims, a major emphasis of the FDA, presents a framework both for instrument selection and for accumulating evidence that the needs of patients and consumers of clinical trial information are being addressed. The drug development process is structured around the package insert listing the indication for a specific therapy and relevant information for the physician and patient regarding dose, proper use, and safety considerations. Approval of a therapy by the FDA hinges on the quality and magnitude of the clinical data supporting the therapeutic claim. Therefore, a clear idea of the proposed target indication or claim must be established first so studies can be designed to support the claim.

The development of a therapy to treat CRF is facilitated by a clear strategy and path for regulatory approval. The Target Product Profile (TPP) is a document that states the proposed claim and goals for the therapy and the target degree of efficacy, safety and dose formulation (63). The TPP is a “living” document that begins with a goal that provides a structure for the design, conduct and analysis of clinical trials within the company and for discussions with regulatory authorities; this document also evolves as new data are acquired. A key component of the TPP is the proposed promotional claims (what the therapy is intended to do) which require careful description of the intended patient population and the type of data that will support the claim.

A pharmaceutical company with a product targeted to alleviate CRF must grapple with definition and measurement issues because CRF has been defined in various ways. The definition of CRF has important implications for the selection of measures and the nature of the data generated to support a therapeutic claim. For instance, if CRF is defined simply as the sensation of tiredness, then evidence of effect based on a single assessment measure (such as the 0-10 scale) may be adequate. If CRF is defined as a symptom with multiple components, then the claim would require consistent effects across all components and may require data from several assessment tools. The FDA now requires a conceptual framework diagram of a symptom measure that explicitly defines the concept measured by the

instrument with a description of the relationships between items, subconcepts, and concept (4).

To appreciate the implications of definition and conceptual framework for measurement, consider the example of therapies for migraine. Migraine is a multidimensional condition with at least four components – pain, nausea/vomiting, phonophobia and photophobia. In order to justify the claim of "relief of migraine", a therapy would have to show effects on all four components. Improvement in only one aspect of the condition would lead to a very limited claim (e.g. relief of nausea associated with migraine) that may have little clinical utility. Applying this analogy to CRF, therapy developers must present a clear conceptual framework of the dimensionality of CRF or how its components respond to treatment in order to propose an appropriate claim.

Selection of the patient population for study is critical to the ultimate claim allowed. Cancer diagnosis or cancer therapy as well as time from diagnosis or last therapy could influence the structure of the claim being sought. Other causes of fatigue such as concomitant depression or mood disorders, anemia, surgery, concomitant medication, radiotherapy and concomitant noncancer medical disorders must be controlled in the study design and/or measured so they could be addressed in the analysis. The FDA now requires that measures of patient-reported outcomes such as CRF have evidence of content validity that is specific to the population, condition, and treatment to be studied (4).

Because CRF severity can vary considerably, it is important to determine up-front what degree CRF is clinically appropriate for treatment and the amount of relief that should be interpreted as treatment benefit (responder definition). The FDA requires that the responder definition be determined empirically. Alternatively, the therapy developer may use anchor-based or distribution-based approaches to define meaningful change in CRF (4).

Treatments for most conditions are associated with the risk of adverse events. A patient's ability to tolerate toxicity of a given therapy will depend on the severity of the CRF and the degree of relief that is expected. In the condition of severe CRF and the promise of significant benefit from treatment, the presence of some toxicity is likely to be better tolerated than when the less benefit is expected. Improvement of CRF is desirable, but improvement in functioning may be an equally relevant clinical outcome.

Conclusions and Future Directions

This report on the measurement of CRF represents the discussion and consensus of a broad-based group including individuals from academia, the pharmaceutical industry, and government. Notably, the ASCPRO group reached consensus on a definition and conceptual model for CRF. The group also agreed that there exist a considerable number of CRF measures that meet "good measure" criteria with strong evidence that they capture the critical elements of the subjective experience of CRF. However, there are issues that still need to be addressed:

- The question of what constitutes a clinically relevant difference or change in CRF has not been answered definitively. There has been considerable work by the scientific community on minimally important differences (MID) in CRF (64-66). The FDA guidance document proposes the use of responder analysis and cumulative response functions as appropriate ways to address this question (4). However, there have been no comparisons of these alternative approaches to determine the advantages and disadvantages of each.

- Sophisticated methodologies such as area under the curve (AUC) and longitudinal growth models have been developed to model change over time and overcome the challenges of missing data. The time is right to implement and evaluate these approaches in the study of CRF. Future research should longitudinally model the complex manifestations of CRF across different disease conditions and the continuum of cancer care from diagnosis, through treatment, to survivorship and end of life.
- In this paper we have made the argument that CRF differs fundamentally from the fatigue of healthy individuals. However, we know little about similarities and differences between CRF and pathological fatigue in other diseases (such as rheumatoid disorders, multiple sclerosis, post-polio syndrome, and chronic fatigue disorder). A compelling question is whether there is sufficient conceptual similarity in patient-reported fatigue associated with each of these disease states (despite obvious differences in etiology) to allow the use of standardized fatigue measures across diseases.

The use of patient-reported CRF as a clinical trial outcome continues to be an evolving field requiring more systematic study. An important goal is to build on the consensus achieved by ASCPRO and other groups such as NCCN, the Oncology Nursing Society, and the Multinational Association for Supportive Care in Cancer (MASCC) so that new therapies for CRF can be developed and evaluated.

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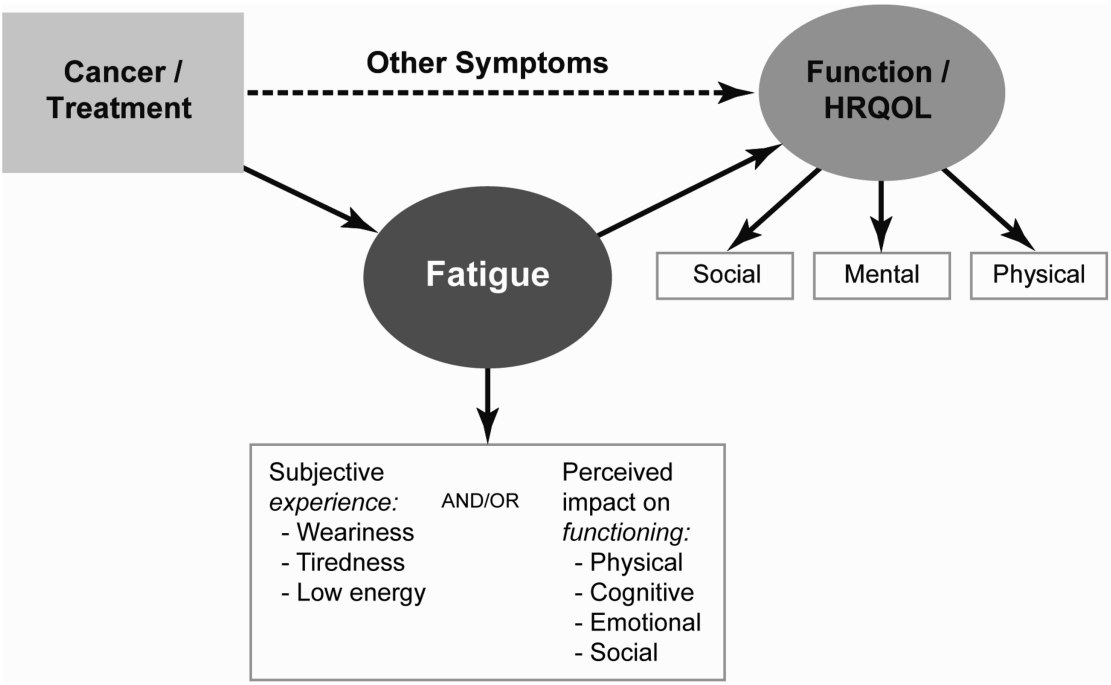

Fig. 1.
ASCPRO Conceptual Model of Cancer-related Fatigue

Table 1

Characteristics of Fatigue

Characteristic	Terms Indicative of the Characteristic	% Definitions Including Characteristic
Subjective	Self-report; self-perception	58%
Physical sensation	Severity of sensations including exhaustion; decreased energy; weakness; malaise; tiredness; lassitude	92%
Unusual	unrelieved by rest; unusual; abnormal; not proportional to activity; unusual need for rest; unpredictable	42%
Impact on functioning	decreased function; decreased capacity for work; decreased quality of life; difficulty completing tasks; poor sleep quality; withdrawal from activities; debilitation	66%
Unpleasant emotions	helplessness; vulnerability; distress; reactivity; impatience; anxiety, emotional numbness; unpleasant experience; emotional lability	54%
Decreased cognitive ability	decreased attention; decreased concentration; decreased motivation; memory deficits; decreased mental capacity; decreased capacity for mental work	46%
Temporal variability	pervasive; chronic; acute; persistent; episodic	58%

Table 2

Patient-Reported Outcome Measures of Cancer-Related Fatigue Implemented in Oncology Trials

Instrument Title (Abbreviation)	No. of Items	Response Scale	Recall Period	Subscales/Factors Described by Authors
Brief Fatigue Inventory (BFI) (67)	9	0-10 numeric rating (Bipolar end anchor descriptions)	Past 24 hrs (8) or Past week (1)	Severity; Interference
Cancer Fatigue Scale (CFS) (20)	15	5-point Likert (Not at all – Very much)	Right now	Physical; Cognitive; Affective
Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-F or FACT-F) (68)	13	5-point Likert (Not at all – Very much)	Past 7 days	Tiredness; Weakness; Difficulty with usual activities
Fatigue Symptom Inventory (FSI) (48)	14	0-10 numeric rating (Bipolar end anchor descriptions)	Past week	Severity; Frequency; Diurnal variation; Interference
Fatigue Severity Scale (FSS) (69)	9	1-7 numeric rating scale (Agreement with statements)	No time frame specified	Fatigue severity
Lee Fatigue Scale or Visual Analogue Scale – Fatigue (LFS) (70)	18	100 mm. Visual analog (Bipolar end anchor descriptions)	Right now	Fatigue; Energy
Multidimensional Assessment of Fatigue (MAF) (71)	16	14 items: 100 mm. visual analog scale; 2 items: Multiple choice	Past week	Degree; Severity; Distress; Impact on activities; Timing
Multidimensional Fatigue Inventory (MFI-20) (72)	20	7-point scale, (Yes, that is true - No, that is not true)	Previous days	General, Physical, Mental Fatigue; Reduced activity; Reduced motivation
Multidimensional Fatigue Symptom Inventory (MFSI) (73)	83	5-point Likert (Not at all – Extremely)	Past 7 days	General fatigue; Physical fatigue; Emotional fatigue; Mental fatigue; Vigor
Profile of Mood States Fatigue Subscale (POMS-F)	7	5-point Likert (Not at all – Extremely)	Past week	Fatigue severity
Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Forms (55)	4, 6, 7 or 8	5-point Likert (Never - Always)	Past 7 days	General fatigue; subjective experience; impact on functioning
Quality of Life Questionnaire Core 30 Fatigue Items (EORTC QLQ-C30) (50)	3	4-point Likert (Not at all – Very much)	Past week	Physical Fatigue
Revised Piper Fatigue Scale (PFS) (22)	22	0-10 numeric rating (Bipolar end anchor descriptions)	Now or today	Behavioral/severity; Affective meaning; Sensory; Cognitive/mood
Rhoten Fatigue Scale (RFS) (74)	1	11-point VAS (verbal anchors)	Present time	Fatigue severity
Schwartz Cancer Fatigue Scale (SCFS) (23)	28	5-point Likert (Not at all – Extremely)	Past 2-3 days	Physical; Emotional; Cognitive; Temporal
SF-36 Vitality Subscale (75)	3	6-point Likert Scale (None of the time – All the	Past week	Vitality

Instrument Title (Abbreviation)	No. of Items	Response Scale	Recall Period	Subscales/Factors Described by Authors
		time)		

Table 3

Desirable Attributes of a Self-Report Measure of Fatigue

Based on a *definition that reflects the construct of fatigue as experienced and perceived by cancer patients*; includes scale(s) that reflect the attributes of the fatigue definition.
Uses appropriate methods to establish *content validity* (i.e., measurement of appropriate content and representation of fatigue attributes).
Has evidence to support *construct validity* (convergent validity, known-group validity, responsiveness).
Provides an *appropriate reference period* to capture the fatigue experience in the study sample.
Meets minimal standards of *precision* for group-level comparisons and is appropriate for measuring fatigue in the target population.
Produces scores that are *interpretable to decision-makers*. Established minimally important differences (MIDs) are valuable.
Incurs minimal respondent burden in terms of length and comprehensibility for people of low literacy and non-native English speakers.
Is translated into multiple languages for multi-national trials with evidence to support measurement equivalence across different translations and across different cultures.
Is available in alternate modes of administration with evidence to support measurement equivalence.
Minimal barriers to access, administer and score the instrument.

Note: Source for information included the Scientific Advisory Committee of the Medical Outcomes Trust (76).