Introduction
Cancer-related fatigue (CRF) is the most common and distressing symptom related to cancer and its treatment. CRF is known to adversely affect quality of life and it is emerging as a dose limiting toxicity associated with the newer targeted agents, limiting the study of potentially effective new combination therapies. Because of its prevalence and impact, CRF has been the subject of much research. The CTriP meeting was held to identify gaps in our knowledge about CRF and develop a focused agenda to advance the science of symptom intervention. Sessions addressed the epidemiology, measurement, and biology of CRF; interventions for managing it; and methods for studying it. Recommendations are grouped within each content area. An additional set of recommendations for “infrastructure development” emerged during the meeting.

Epidemiology, Measurement, and Biology of CRF
Consensus has not been reached about the definition of cancer-related fatigue or its essential components. Debate continues as to whether CRF is a definable syndrome or a symptom with degrees of severity. CRF has alternately been understood as a subjective symptom experience, an objective phenomenon (i.e., muscle weakness), or as a diagnosable syndrome.

Each definition has implications for measurement. Numerous subjective measures of fatigue have been developed, but no gold standard has emerged. Measurement of muscle weakness has not been a useful CRF indicator. An ICD-10 diagnosis of CRF has been proposed but further evaluation is needed.

The underlying biological mechanisms of CRF are not well understood although there is consensus among experts that both physiological and psychosocial factors contribute to its onset and/or maintenance. For example, studies consistently find associations between fatigue and mood disturbance. Mounting evidence has begun to shed light on inflammatory responses and adrenal dysregulation as possible biological mechanisms for CRF [1]. Some studies have shown an association between inflammatory markers and fatigue before treatment, during radiotherapy or chemotherapy, and during the survivorship period. Given that these potential biological mechanisms have been shown to be affected by stress and other psychosocial factors, it is likely that CRF will be best addressed by multi-dimensional models.

Pharmacological and Non-pharmacological Interventions for CRF
Several pharmacologic and non-pharmacologic interventions have been evaluated for the alleviation of CRF; however, there is no consensus on treatment at this time. A recent meta-analysis of pharmacological treatment [2] showed that methylphenidate and erythropoietin were superior to placebo; however, gestational steroids and paroxetine were not effective. With regard to non-pharmacologic intervention studies, both psychosocial and exercise interventions had effect sizes that were significant and clinically meaningful in reducing CRF [3]. Because CRF is a multi-factorial problem with many potential triggers, mechanisms, and impacts, multi-component interventions need to be evaluated for its management.
Design, Methods, and Statistics
A number of design and analysis issues were raised in the context of subjective symptom studies. Questions still remain about the appropriate control of confounding variables in CRF research and the identification of innovative approaches for its study.

Recommendations for Clinical Trials Planning
Definition, Epidemiology, and Biology of CRF
- Come to agreement on a basic definition and components of CRF.
- Differentiate CRF from other symptoms with overlapping components (such as depression and sleep disturbance).
- Develop research-based case definition(s) of CRF including clinical subtypes.
- Study host, disease, treatment, and environmental factors that result in different manifestations of CRF.
- Identify high priority diseases (such as Hodgkins lymphoma or head and neck cancer) and treatments (such as tyrosine kinase inhibitors) for which the study of CRF is critical.
- Conduct studies that examine the potential bio-psycho-social mechanisms of CRF including:
  - Circadian and sleep rhythms
  - Inflammatory response
  - Gluco-corticoid pathways
  - Genetic influences
- Conduct comparison studies to examine similarities and differences between CRF and fatigue in other diseases (such as fibromyalgia or chronic fatigue syndrome).

Measurement
- Come to agreement on a set of common core CRF measures (such as 0-10 numeric rating, PROMIS, and/or PRO-CTCAE) in all clinical trials in which CRF is an endpoint to build a large data set for comparisons across trials.
- Come to agreement on core biological measures and standard times of measurement across trials.
- Consider PRO measurement strategies to capture changes in CRF over time including daily diaries and use of devices and technology (such as actigraphs, computers, handheld devices).
- Convene a meeting on patient-reported outcomes (PRO) to address selection and implementation of common measures in CCOP trials and identify other symptoms that should be measured in association with CRF.
- Develop more precise evidence-based interpretation of PRO scores for CRF (such as cut scores for low, moderate, and high fatigue; minimally important differences)

Pharmacological and Non-pharmacological Interventions for CRF
- Develop large exercise intervention trials in the CCOP setting considering:
  - Survivors as a model
  - Safety issues, climate, and toxicities of treatment
  - Intervention practicality and exportability
  - Motivation as a key factor related to uptake of intervention.
- Conduct a large trial to confirm the effect of modafinil in treating CRF.
- Conduct large clinical trial(s) of methylphenidate
  - Overcome barriers to the study of controlled substances
- Explore old drugs for new purposes (such as broad-spectrum antidepressants).
• Develop studies of interventions to restore mind-body balance (such as yoga and other relaxation techniques).
• Tailor interventions to individual characteristics including:
  - host factors that could influence response to intervention (such as age, gender, comorbidities, etc.)
  - the effect of the person conducting the intervention
• Conduct a multi-component intervention (such as yoga plus modafinil) that is powered for sub-group analysis so effective intervention components can be identified.
• Conduct intervention studies that also examine potential biological mechanisms.

**Design, Methods, and Statistics:**
• Consider defining CRF severity as eligibility criterion for clinical intervention trials.
• Conduct longitudinal studies to examine the natural history of CRF from diagnosis, through treatment, and into survivorship.
• Use mixed quantitative and qualitative methods to gain a better understanding of the individual's experience of CRF and the perceived benefit of the intervention being evaluated.
• Consider novel study designs such as doubly randomized preference trials.

**Infrastructure Development:**
• Develop collaborations with organizations concerned about symptom management (MASCC, ISOQOL, ASCO, etc.) to better organize the study of CRF.
• Develop collaborations with basic scientists working with animal models to stimulate research and modify methods to address clinical concerns (such as repeated drug administration as a simulation of cyclic chemotherapy in humans).
• Develop translational science partnerships between cooperative group and investigator-initiated projects.
• Develop partnerships with patient advocacy organizations to better understand patient/survivor priorities and desired outcomes.
• Develop a registry of clinical trials using common biological and patient reported outcome (PRO) measures of CRF
• Develop multiple funding mechanisms for research (such as government, private industry, and international RFAs) to conduct long-term follow-up of adults/children with CRF.
• Develop funding mechanisms (such as career development awards) to interest junior faculty (including basic scientists and oncology clinicians) in the science of symptom management.
• Set up standard laboratories for CCOP trials to collect, analyze, and store specimens.
LITERATURE CITED

