NCI Symptom Management and Quality of Life Steering Committee
Clinical Trials Planning Meeting Summary

Building Bridges: the Identification of Core Symptom and Health-Related Quality of Life Domains for use in Cancer Research

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Goals

The Symptom Management and Health Related Quality of Life Steering Committee held a one and a half day clinical trials planning meeting to:

1) **Identify a standard core set of patient-reported outcomes (PROs) including symptoms and/or health-related quality of life (HRQOL) domains to be assessed in clinical trials with cancer patients.** Selected symptom and HRQOL domains should be ones that are commonly experienced across cancers and are helpful to inform clinical research findings and policy decisions. For example, cancer patients in general experience depressive symptoms, anxiety, sleep disturbance, and fatigue; thus, these symptoms may be selected as core domains.

2) **Identify a core set of symptoms and/or HRQOL domains that should be assessed in clinical trials that include patients with either a head and neck cancer, prostate cancer, or gynecological cancer.** These cancers were selected because their treatments are multi-modal and both the disease and treatments have significant effects on a patient's quality of life. For example, in prostate cancer, specific HRQOL domains selected may include bowel functioning, urinary obstruction, urinary incontinence, and sexual functioning.

To accomplish this goal, a group of experts in PRO measurement, experts in the use of PROs in cooperative group trials, Disease Site Chairs and Symptom Management Quality of Life Liaisons of the NCI Steering Committees, Cooperative Group Chairs, pharmaceutical PRO experts, FDA representatives, and NCI representatives, as well as patient advocates were brought together. The proposed deliverables from this meeting were a listing of core domains to be collected specific to the conditions experienced by individuals with head and neck cancers, prostate cancer, and gynecological cancers, and core domains to be collected across all cancers and/or by treatment type. With each core domain, links were to have been provided to existing questionnaires that could be successfully used with cancer patients. This proposed resource would have incredible value for investigators to save them time for searching for this information and to provide a link to review committees to support their selection of both endpoints and measures. Thus, the products from this meeting will set forth a future research agenda for greater integration of PRO measures in cancer research. This effort was proposed to lead to at least one publication and provide guidance to DSSC of key PROs to consider when designing treatment trials that include a PRO or HRQOL domain.

Background Justification

In 2001, the NCI created the Cancer Outcomes Measurement Working Group (COMWG) consisting of 35 experts convened to examine the state of the science and identify future priorities for outcomes assessment in cancer research. After an extensive review of the cancer outcomes research field over the previous two decades, the COMWG, found that assessing health-related quality of life (HRQOL) and symptom burden is feasible using questionnaires that meet established criteria for reliability and validity.

Building on the COMWG findings, the NCI sponsored an international conference in 2006 entitled, "*Patient-Reported Outcomes Assessment in Cancer Trials (PROACT): Evaluating and Enhancing the Payoff to Decision Making*." The meeting resulted in a 2007 JCO monograph which identified significant issues and challenges for the incorporation of patient-reported outcomes (PROs: includes HRQOL and symptom burden) in cooperative group trials. Among them was the recognition of the potential for patient-reported symptoms to enhance adverse event monitoring in cancer trials.

Both the COMWG and PROACT reported that a key impediment to move the field forward is a lack of universally recognized standard set of PRO domains to routinely be collected in cancer trials. Clinical trial investigators struggle with the task of knowing what domains to measure in their study that would inform the understanding of the safety and efficacy of the intervention under investigation. The literature is vast on this topic, yet there lacks one source where consensus has been reached on the key PRO domains. As a result, investigators may drop consideration of a PRO endpoint or spend significant time up front to review the literature, consult with co-investigators, and agree on measured endpoints. Further, there lacks consistency from one study to the next on what PRO endpoints are measured which reduces our ability to compare or combine results across trials. Thus, identification of a core set of PRO domains has multiple advantages:

1) Enables clinical trial investigators to come to one source to know what HRQOL and symptom domains to include in their study. This source document will list which domains need to be assessed by cancer type and/or treatment mode and associated questionnaires that measure the domain.

2) Allows researchers and funding agencies to identify domains that lack good quality measures or identify existing questionnaires that require more validation evidence for use in clinical trials. This will lead to a research agenda for measures development and validation in NCI-sponsored trials.

3) Identifying a core set of data elements will facilitate comparison and combination of data across research studies around the world. This is in line with CaBIG and other bio-

informatic database initiatives to identify common data elements for meta-analysis types of studies.

The result of this exercise would be a greater uptake of PRO measures in clinical trials. Further, this will harmonize the cancer research field by building a common language to communicate across investigators and Federal agencies. This also directly responds to the recent Institute of Medicine (IOM) report on clinical trials. IOM recommendation # 3 deals with harmonization of common aspects of clinical trial conduct. The rationale states, "Defining a core set of data elements, along with guidance on how those elements could be modified under certain circumstances, would speed the FDA review process and lead to greater uniformity in data requirements." (Nass, Moses, & Mendelsohn, 2010, page 21)

The timing for this Clinical Trials Planning (CTrP) Meeting on *Building Bridges: the Identification of Core Symptom and Health-Related Quality of Life Domains for use in Cancer Research* is positioned perfectly to take stock of a number of initiatives funded by the NCI and NIH to develop standardized measures of patient reported HRQOL and symptoms, and guidance recently released by the FDA:

1) The NIH funded Patient-Reported Outcomes Measurement Information System (PROMIS) network was set up in 2004 to provide researchers access to efficient, precise, and valid measures of HRQOL and symptom burden. Available to the public, the PROMIS serves as a valuable resource for providing standardized endpoints for outcomes commonly experienced by cancer patients including fatigue, pain, depression, anxiety, sexual function, sleep disturbance, and perceived cognitive abilities. The NCI has made the PROMIS a high priority by supporting several grants that validate the use of PROMIS measures in different cancer types, across the disease continuum, and in different race/ethnicities.

2) In 2008, the NCI funded the development of the PRO-CTCAE to provide complimentary patient responses to experienced symptomatic adverse events captured in CTCAE. Twenty of the 81 symptoms currently included in the PRO-CTCAE have been identified as core symptoms that most cancer patients experience. NCI is building and testing this system with the goal to integrate the system in all clinical trials sponsored by NCI. Routine collection of common PRO-CTCAE data elements will enhance toxicity monitoring and will facilitate collection of common data across clinical studies to build a proactive surveillance system and allow comparative effectiveness research studies using the combined datasets.

3) In 2009, the FDA released its final guidance to industry on *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. In the guidance, the FDA sets down principles and criteria for the use of a PRO instrument for making drug labeling claims. As a result of the guidance, researchers have been re-evaluating existing questionnaires to make sure the instruments are valid for capturing the PRO domain of interest. It has also alerted the field to think carefully

about the endpoints that are selected for use in a trial; thus furthering the need for the guidance to come out of this NCI Clinical Trials Planning meeting.

4) With release of the FDA guidance, the FDA also established the PRO Consortium with the mission to establish and maintain a collaborative framework with appropriate industry stakeholders for the development of qualified, publicly available PRO instruments for use in clinical trials where PRO endpoints are used to support product labeling claims. Part of the activities of the group is to identify priorities for the development of new PRO measures where gaps have been recognized by consortium members.

In addition, insight will be gained by the experiences of the European Organization for the Research and Treatment of Cancer (EORTC) and the National Cancer Institute-Canada who automatically include a baseline measure of patient-reported HRQOL with use of the EORTC-QLQ-C30 (unless justification has been made that HRQOL data is not critical to the trial). Standardized data collection by these organizations has enabled them to carry out large meta-analysis studies across its trials.

Despite the extensive literature and focus on PRO measurement, identifying the core HRQOL and symptom domains will not be an easy task as a number of critical issues will need to be resolved including how to balance the need for a comprehensive set of indicators of HRQOL and symptoms versus the time and budget burden of administering long questionnaires, how many domains to be considered as a “generic” core to be collected across cancer types versus those specific to a cancer type or treatment condition, and how to balance information for adverse event monitoring versus exploratory or primary/secondary endpoints in a trial. To meet our goals for a one day CTrP meeting, we will focus on three cancer types that present unique challenges for identifying core domains: Head and Neck Cancers, Gynecological Cancers, and Prostate Cancer. Each of these has critical need for PROs as treatments are multi-modal and have significant effects associated with the treatments that affect safety and efficacy of the intervention.

Objectives

- Identify a core set of PRO domains that should be assessed in clinical trials with cancer patients.
- Identify a core set of PRO domains within head and neck, prostate, and gynecologic cancers that will be incorporated in clinical trials.
- Recommend approaches for incorporating the core PRO domains into common CRFs. As clinical trial data collection moves toward implementing a standard electronic data capture system, PROs need to be included in this effort so they will be more easily integrated within trials.

Outcomes:

1. Recommended Core Set of Limited PRO Domains for Collection Across all Clinical Trials that Utilize a PRO. Core set includes 12 symptoms be measured, specifically fatigue, insomnia, pain, anorexia, dyspnea, cognitive problems, anxiety/worry, nausea, depression, sensory neuropathy, constipation, and diarrhea. This core set is neither exhaustive nor fully inclusive of the symptoms that might be studied in any particular trial.

2. Recommended Disease Core Set of Site Specific Symptoms and/or HRQOL Domains for Head and Neck Cancer, Prostate Cancer and Ovarian Cancer

    a. Ovarian Cancer: abdominal core, neuropathy, fear of recurrence, sexual function, overall HRQOL
    b. Prostate Cancer: urinary incontinence, urinary obstruction, bowel function, sexual dysfunction, hormonal symptoms
    c. Head & Neck Cancer: swallowing, oral pain, dry mouth, dental health, taste, opening mouth, shoulder function, social function

Actions:

- A resource document will be created that will list the core PRO symptoms to be considered in any trial including a PRO with cancer patients and specific PRO domains to be assessed within head and neck cancers, prostate cancer, and gynecologic cancers.
    - This resource will include a list of available PRO measures that capture the domains of interest and be disseminated to the research community.

- Continue to Emphasize the Importance of Hypothesis-Driven Inclusion of PROs in cancer treatment trials

- Disseminate the recommended core domains as stated above
    - Publish- 4 papers
        - Current plans are for combined journal submission by late spring 2013
    - Present to Steering Committee Chairs:
        - Conference Call set for March 22, 2013
    - Work with Steering Committees & Cooperative Groups to implement recommendations