EDITORIAL

Core Symptom Measures in Cancer Clinical Trials

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Some of the most exciting recent advances in cancer research have come from learning more about how diverse a disease "cancer" actually is. For example, genomic analysis has identified at least 10 subtypes of breast cancer, with implications for varying therapeutic approaches (1). Against this backdrop, the set of four papers in the current issue of the Journal take a seemingly opposite approach: seeking commonality in symptom assessment across cancers, with the aim of identifying a core set of symptoms for use in clinical trials (2–5).

The four papers have slightly different emphases, all focusing on identifying core symptoms in: different cancers (2), prostate cancer (3), head and neck cancer (4), and ovarian cancer (5). The authors comprise some of the most respected researchers in the quality of life (QoL) and cancer field, and their desire to promote assessment of cancer-related symptoms in clinical trials is laudable.

Research in patient-reported outcomes (PROs), which includes QoL and symptom assessment, has advanced considerably in recent decades, such that validated self-report questionnaires are available and widely used in cancer clinical trials. Cancer-specific questionnaires such as the EORTC-C30 (6) and the FACT (7) are conceptually based and provide parsimonious assessments of domains of well being (eg, physical and social functioning) and specific symptoms. In addition, both of these questionnaires have validated modules with items (including symptoms) specific to prostate, head and neck, and ovarian cancer. It is unclear what gaps the authors see in the current tools, and what they are trying to accomplish by extracting some items from these questionnaires and adding one more. Of the proposed core symptoms, it appears that only "sensory neuropathy" is not included in the EORTC-C30 and/or the FACT.

The discussion is clouded by the authors' reference to a "core set of symptoms and/or health-related (HRQOL) domains" (2), a conflation that is repeated in each paper (3–5). It's not clear what the authors mean by a "symptom," since this term is not defined, and some of the items listed as symptoms, such as dental health (4) and weight loss or weight gain (5), would appear to be more appropriately measured by objective assessments than by PROs. Further, what is a "symptom" compared to a "domain"? And what is the relationship between symptoms and domains? Fayers has long contended (8) that symptoms that are important to consider vary according to the diagnosis and treatment, and this hypothesis has received empirical support (9). As such, distinguishing between symptoms and domains is very important.

Although the papers' objective is to promote a consistent approach to assessment across trials and cancers, the articles do not provide a compelling rationale for how a core set of items will advance the field. For (hypothetical) example, why would knowing that ovarian cancer patients experience more anxiety than prostate cancer patients be important to inform trial outcomes? As the authors of the prostate cancer paper point out (3), comparing PROs across therapies such as radical prostatectomy and radiation is not always useful, given that patient characteristics drive both the selection of the appropriate therapy and the PRO concerns that are most salient.

Phase III clinical trials of cancer therapies, the most common type of trial that includes PROs, usually assess differences between two or more cancer treatments. Many of the core items proposed eg, anxiety, fear of recurrence, mental well being—are (with some possible exceptions) more likely to reflect overall responses to cancer and treatment rather than differences between therapies, which often require targeted questions specific to the particular agents or modalities under study.

Consistent with clinical trials methodology, it seems reasonable that symptoms, like other endpoints, should be assessed when they are relevant to trial aims and the patient population under study. The authors provide no compelling rationale for why a core set of symptoms should be assessed in every trial, regardless of whether this contributes to the aims of a given study. The Reeve et al. abstract recommends that 12 core symptoms should always be measured, but the authors also state that endpoints "should be well-justified, hypothesis-driven, and meaningful to patients" (2). It would be a rare clinical trial that included hypotheses for 12 different symptoms.

Cancer is changing-both in terms of patient characteristics and cancer therapies-and these changes present many exciting opportunities for cancer symptom researchers. For example, cancer patients are getting older and will continue to do so at least until the end of the baby boomer generation; what does comorbidity common in older people mean for symptom assessment? As mentioned briefly, the dramatic recent increase in HPV-related cancers has led to many changes in head and neck cancers-eg, pathology, stage of disease, treatment, and patient attributes, including socioeconomic, health behavior, and risk factor profiles (4). Many future head and neck patients are likely to have different symptom profiles from those in the past, and more attention is needed now to understand how to assess their symptomatology and needs. Therapies are also changing. As the authors of the ovarian paper point out, there are virtually no data available on PROs and biologics, yet such therapies are key to the future in this disease and learning how to measure their impact on patients is an emerging priority (5).

PRO researchers need to build on what has been accomplished, while being responsive to advances in research methodology (eg,

computer adaptive testing, item response theory), new technology (eg, smartphones and apps that enable continuous monitoring of self reports, behaviors, and biological indicators), and changes in the cancer and health care landscapes. In the clinical trial context, PRO outcome assessment requires tailoring to the research question under investigation. It's not clear that using core measures is necessary or sufficient to provide the specificity required to answer trial questions, nor that "core symptom scores" across trials are interpretable or make a contribution to cancer control. The development of a library of well-validated assessments for a range of cancer symptoms, from which investigators could choose what is meaningful for a given trial, would be another way to promoting consistent and appropriate assessment.

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Notes

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